CROONIAN LECTURES

1892

SIR WILLIAM ROBERTS, M.D., F.R.S.

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ON THE

CHEMISTRY AND THERAPEUTICS

OF

URIC ACID GRAVEL

AND

GOUT

BEING THE CROONIAN LECTURES FOR 1892

DELIVERED BEFORE

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BY

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LECTURE I

THE CHEMISTRY OF URIC ACID AND THE URATES—COMPARATIVE PHYSIOLOGY OF URIC ACID

Mr. President and Gentlemen,—The morbid phenomena associated with uric acid divide themselves naturally into those which have reference to gravel and calculus, and those which have reference to gout. In the former, uric acid is thrown down in the free state from the urine as concretions in the urinary channels; in the latter, uric acid is thrown down in a state of combination as sodium bi-urate in the interior tissues of the body. In both conditions the precipitated substance necessarily acts as a foreign body, and tends to cause inflammatory incidents and obstructions in the parts implicated. In regard to gravel and calculus, the whole of the morbid sequences are thus accounted for; no suspicion is entertained that uric acid concretions lodged in the kidneys or bladder produce any disturbances above and beyond those which are due to mechanical injury. But in regard to gout, uric acid is supposed to play a double part. It is commonly believed that, besides the irritation consequent on the precipitation of sodium bi-urate in the joints and elsewhere, uric acid floating in solution in the bodily fluids acts as a true poison; and it is assumed that a large part of the symptoms associated with the gouty state are directly due to this poisonous action. The

soundness of this assumption will be hereafter called in question. It will be shown to be more probable that uric acid does not possess any inherent poisonous quality, and that when mischief arises from it, that mischief is consequent on the acid being precipitated in the solid form as sodium bi-urate in the fluids or tissues of the body. The substantiation of this view would bring gout and uric acid gravel into close parallelism. Gout would then become, like gravel—in so far as its phenomena depend on uric acid, but, of course, no further—a disease of which the manifestations are proximately due to mechanical injury. On this view it becomes evident that the chemical reactions of uric acid and the urates, and especially those reactions which govern the holding in solution of these substances, have a more direct bearing on clinical and pathological problems than those conditions which have reference to the mode of origin of uric acid. In either case, whether uric acid be poisonous or not, the pathological history of uric acid is intimately bound up with its chemical properties, and a knowledge of these properties is an essential pre-requisite for a scientific apprehension of the problems that arise in connection with uric acid gravel and the uratic phenomena of gout.

The amorphous urate deposit of human urine forms a convenient starting point for the study of the pathological chemistry of uric acid. This is the most familiarly known and yet, perhaps, the least understood of all urinary deposits. The amorphous urate is frequently deposited in the urine of perfectly healthy persons, especially in the colder seasons of the year, and at all seasons after sharp exercise and severe sweating. It is also habitually seen in the urine of persons suffering from slight catarrhal conditions or trifling dyspeptic

derangements. Lastly, it is a common accompaniment of pyrexia, and of grave organic wasting diseases of all kinds. The amorphous urate deposit coincides with an acid reaction of the urine, and is never thrown down in a neutral or alkaline urine. It is recognised clinically by its disappearance when the urine is warmed. It is always more or less stained with the proper pigments of the urine, and its tint varies accordingly. Under the microscope it presents a granular appearance, without any obvious crystalline structure. All this is matter of common knowledge. But when we carry our inquiries further and ask: What is the chemical nature of this substance? what are its physiological analogies and pathological relations? no clear answers are forthcoming. Indeed, such questions are nowadays scarcely asked at all. The amorphous urate deposit has for some time past been relegated almost to the position of a clinical curiosity, devoid of any real bearing on pathological and physiological questions. But if it can be shown that this substance is a representative body—that it typifies the exclusive mode in which nitrogen is eliminated in vast tribes of the animal series—that it represents the chemical combination, and the sole combination, in which uric acid subsists normally in the healthy organism, and that, moreover, the pathological troubles connected with uric acid are due to deviations, in one direction or other, from this normal combination—then it becomes obvious that the chemical composition and reactions of the amorphous urate possess a very real interest both for the physician and the biologist. Before entering on this inquiry it is necessary to recall to your memories what is already known and established in regard to the chemistry of uric acid and its combination with bases.

Uric acid is regarded by chemists as a bibasic acid, that is to say, as an acid containing two atoms of replaceable hydrogen. It is represented by the formula $H_2(C_5H_2N_4O_3)$, or more simply as $H_2\bar{u}$. It forms, like other bibasic acids, two regular orders of salts: namely, neutral urates, with the general formula $M_2\bar{u}$; and acid urates, or bi-urates, with the general formula $MH\bar{u}$.

These two orders of uric acid salts were elaborately studied in Liebig's laboratory nearly half a century ago by August Bensch, in collaboration with an English student, Dr. James Allan.[1] So reliable and so complete have these researches been regarded, that no chemist has, so far as I know, thought it necessary to repeat and verify them; and they still constitute our principal source of information with regard to these two classes of salts.

The *neutral urates*, $M_2\bar{u}$, were prepared by Allan and Bensch by dissolving uric acid in cold dilute solutions of the caustic alkalies, free from carbonates, and then boiling down the solutions in a retort until crystals made their appearance. The neutral urates have an intense caustic taste, and are very unstable. They are decomposed by carbonates, and even by the carbonic acid of the air. Of late years these neutral urates have been made to figure prominently in certain theories of gout. According to these theories the neutral urates constitute an essential link in the process which leads up to the formation of gouty deposits. Such theories, however, are, on chemical grounds, untenable. The neutral urates can only be produced in the presence of caustic alkalies, and in the absence of carbonic acid and the carbonates. But caustic alkalies cannot exist in the living organism, and carbonic acid and the carbonates are everywhere present. It would, therefore, seem impossible that the neutral urates

[1] Liebig's *Annalen der Chemie u. Pharm.* vol. lxv. p. 181.

should ever arise or subsist in the living body, or that they should ever play any part in the physiological or pathological history of uric acid. And until it can be demonstrated that these salts do actually exist in the body, or, at least, that they can be formed under conditions which are known to be possible in the living body, it is futile to frame theories in which these compounds are made to intervene. With these remarks, the neutral urates may be absolutely dismissed from our consideration, as having neither part nor lot in the vital history of uric acid, whether in health or in disease.

The *acid urates*, or *bi-urates*, HMŪ, are prepared by dissolving uric acid at a boiling heat in weak solutions of the alkaline bicarbonates. On cooling, an abundant precipitation of bi-urate, in splendid stars and bundles of zeolitic crystals, takes place. The bi-urates are the best known and most stable salts of uric acid. They are sparingly soluble in water, but are not decomposed thereby; and when such solutions are evaporated, the bi-urates are again deposited unchanged. The bi-urates are encountered pathologically in gouty concretions, of which the sodium bi-urate forms the distinctive constituent. The bi-urates are never seen as a deposit in the unchanged urine, neither in health nor in disease; but when the urine undergoes ammoniacal decomposition, the ammonium bi-urate may be occasionally detected in the sediment as minute elongated dumb-bells, mixed with the amorphous phosphate of lime and the ammoniaco-magnesian phosphate which constitute the ordinary sediment of decomposed urines. There is, moreover, no proof that uric acid ever exists as a true bi-urate in solution in normal urine, and evidence will be given later on that when bi-urates are artificially introduced into normal urine they fail to maintain their integrity, and

at once undergo a change of composition. Nor is there any actual proof that uric acid ever exists as a true bi-urate in the healthy blood and interstitial juices. It is, however, susceptible of proof that in certain abnormal circumstances bi-urates can and do arise under conditions which habitually prevail in the living body. For if uric acid be dissolved artificially in healthy blood-serum, crystals of sodium bi-urate will ultimately appear in it. I say ultimately, because, as will hereafter appear, uric acid does not at first enter into solution in blood-serum as true bi-urate, but this state of combination is slowly developed and gradually attained after a certain lapse of time. It may, therefore, be affirmed that the bi-urates, although known to us as pathological products in gouty deposits, are not, strictly speaking, known to us as physiological constituents, neither of the blood nor of the urine. But inasmuch as uric acid in some form of combination or other does exist normally in minute quantities in healthy blood, and exists in much larger quantities in healthy urine, the question arises: What, then, is this other form of combination—this normal and physiological combination, which is neither neutral urate nor bi-urate—in which uric acid exists in the healthy body? This question brings us back to the consideration of the amorphous urate deposit.

REACTIONS OF THE AMORPHOUS URATE DEPOSIT—IDENTITY OF IT WITH THE URINARY EXCRETION OF BIRDS AND SERPENTS

The amorphous urate deposit as we find it in the urine is not a chemically pure article; and not only so, but the urine with which it is mingled entirely masks its most important reactions. In order to study the pro-

perties of this substance it is necessary first of all to separate it from the urine. This is effected by filtering off the sediment and washing it thoroughly on the filter with rectified spirit and then drying it. The deposit is still contaminated with pigment, but it is sufficiently pure for the display of its most striking reaction, and that is, its behaviour with pure water. When the amorphous urate, thus purified, is mixed with a considerable volume of distilled water it is speedily disintegrated. A portion passes into solution in combination with the bases, and the remainder falls down as an insoluble precipitate of crystalline uric acid.[1] This remarkable transformation may be witnessed in progress under the microscope in the following manner. A speck of the purified deposit is intimately mixed on a glass slide with a drop of distilled water and protected with a covering-glass. To keep the preparation thoroughly moist, fresh supplies of water are from time to time insinuated under the covering glass. In the course of five or ten minutes beautiful ovoid crystals of uric acid begin to make their appearance. These grow and multiply until, in the course of half an hour, the entire field of vision is thickly studded with crystals (see fig. 1) ; and the process goes on, provided the preparation be kept from drying, until the amorphous matter seems to be entirely changed into crystals of uric

[1] The effect of water on the amorphous urate was first observed by Berzelius. He noticed that when the amorphous urate sediment was caught on a filter and washed with water, crystals made their appearance. He did not, however, appreciate the significance of this result, and supposed that the crystals were composed of urate of ammonia. Subsequently Lehmann made a similar observation, and identified the crystals as uric acid. He attributed the liberation of the uric acid, not to the action of the water, but to a change set up by the colouring matter. The real nature of the reaction was first demonstrated by Bence Jones, as will be presently explained.

acid. The reaction here described may, according to my experience, be always demonstrated with every freshly-collected sample of amorphous urate deposit. The rate of transformation varies a good deal. With fawn-coloured deposits the change is usually completed in from fifteen to twenty minutes ; with the more deeply tinted deposits the time is longer, and extends to half an hour or an hour.[1]

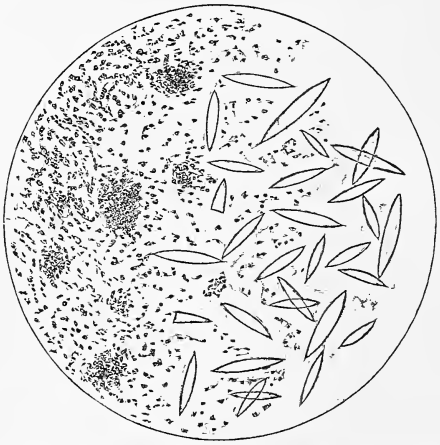

FIG. 1.—Showing the action of water on purified amorphous urate deposit.

The interest attaching to the amorphous urate deposit is greatly enhanced when we learn that the urinary excretion of birds and serpents displays identically the same reactions as the amorphous urate.

The white mortar-like substance which constitutes the urinary excretion of birds and serpents is usually

[1] In performing this experiment it is desirable to use distilled water, but ordinary potable water generally answers the purpose. Some potable waters, however, have a slight alkaline reaction from the presence of bicarbonate of lime; when this is the case, the experiment is liable to miscarry or to succeed imperfectly.

described as consisting of bi-urate of ammonia. This view is, however, based on a fallacy. The misapprehension has arisen from the excretion having been examined, not in the unaltered state, but after it had undergone secondary changes subsequent to its emission, either through bacterial decomposition or through contact with water. If the excretion be examined in the fresh and uncontaminated state, it is seen under the micro-

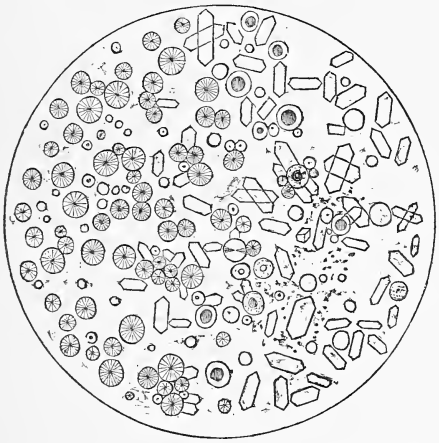

Fig. 2.—Urinary excretion of the boa. The left-hand portion shows the unaltered spheres, the right-hand portion shows the action of water on the excretion.

scope to consist of minute spheres (fig. 2) about the size of the white corpuscles of the blood. Some are twice this size, and a great many are much smaller. These spheres exhibit a radiated crystalline structure, and display a black cross with polarised light. When tested under the microscope with a drop of distilled water, in the manner before described in the case of the amorphous urate, the spheres are seen to gradually melt away with abundant emission of colourless hexagonal tablets of uric acid.

When the excretion is treated with a large volume of water in a beaker, a portion goes into solution as bi-urate, and the rest falls down as crystals of uric acid. In short, the urine of birds and serpents reacts with water precisely in the same way as the amorphous urate sediment, except that the transformation takes place more rapidly. It can, moreover, be shown that the difference in physical form between the two substances is a mere accident of molecular aggregation. For under certain conditions, as will be presently shown, the amorphous urate deposit can be obtained in regular crystalline spheres, scarcely distinguishable from the spheres of the urine of birds and serpents; and, conversely, if the urine of birds or serpents be dissolved in hot normal urine, and the solution be then rapidly cooled, the substance is re-precipitated as an amorphous tinted deposit undistinguishable from the amorphous urate sediment. These observations point to the conclusion that the amorphous urate deposit of human urine and the solid, or semi-solid, urinary excrement of birds and serpents are essentially one and the same substance. And the question arises: What is the constitution of this substance? Is it merely a mechanical mixture of bi-urate with varying quantities of free uric acid, or is it a definite chemical combination, representative of a new and third order of uric acid salts, differing essentially from the two regular orders previously recognised? The elucidation of this question involved a somewhat protracted inquiry, to which I must now ask your patient attention.

CHEMICAL CONSTITUTION OF THE AMORPHOUS URATE DEPOSIT AND OF THE URINARY EXCRETION OF BIRDS AND SERPENTS—THE EXISTENCE OF A THIRD ORDER OF URIC ACID SALTS, OR QUADRI-URATES

We are indebted to a former distinguished Fellow of this College, Dr. Bence Jones, who was, moreover, one of my predecessors in this office of Croonian Lecturer, for the first real light on the chemical constitution of the amorphous urate deposit. His researches were published in the *Journal of the Chemical Society* for 1862.[1] He there describes the action of water on the amorphous urate sediment. He shows that the portion of the sediment which is not dissolved by the water is pure uric acid, and that the portion which goes into solution is true bi-urate. He next gives the results of a quantitative analysis of three samples of the amorphous urate sediment, made especially with the object of ascertaining the proportion of uric acid to the quantities of the bases contained in them. He found in each sample that the uric acid was in excess of the quantity required to form bi-urates with the bases present. The proportion of this excess varied greatly in the three samples; but when the three analyses were thrown together, and the average struck, the mean amount of uric acid was found to be almost exactly double that required to form bi-urates with the sum of the bases present. He also calculated the corresponding proportions in four similar analyses previously made by Scherer. Here likewise the separate analyses gave the most discordant proportions; but,

[1] 'On the Composition of the Amorphous Deposit of Urates in Healthy Urine,' by Henry Bence Jones, *Journal of the Chemical Society*, 1862, vol. xv. p. 201.

again, it so fell out that the average of the whole four analyses yielded a proportion of uric acid which was very nearly double the amount required to form bi-urates with the sum of the bases. These closely-approximating averages, although drawn from numbers so divergent that their agreement could obviously only be due to a fortuitous coincidence, seem to have inspired Bence Jones with the happy conjecture that there existed a third order of uric acid salts, of more complex constitution than the two previously known, in which an atom of bi-urate was loosely combined with an additional atom of uric acid. And he drew the inference that the amorphous urate deposit consisted of, or at least often contained, such a combination.

In order to test the soundness of this conjecture he sought to form an artificial sediment of urates which, when treated with water, would, like the amorphous urate deposit, be disintegrated into free uric acid and bi-urate. In this attempt he succeeded both with potash and soda. By dissolving uric acid in potash or soda ley, and then carefully adding acetic acid (or phosphoric acid) until the liquid became slightly acid, he obtained a dense white precipitate. This was caught on a filter, washed with alcohol, and dried. This substance was found to possess the characteristic properties of the amorphous urate deposit. It was granular in character, and was decomposed by water with abundant emission of uric acid crystals. He made a quantitative analysis of two samples of the potash compound thus obtained. He found that the portion that went into solution when the substance was treated with water corresponded exactly with the theoretical formula of potassium bi-urate; and that the uric acid which remained undissolved approximated in amount to that which went into

solution as bi-urate. Commenting on these results he says:—'It appears from these experiments that an artificial granular deposit may be formed, which is decomposed by washing with cold water, or by boiling, into uric acid and acid urate of potassium. This granular substance may be considered to resemble the quadroxalate of potassa, which differs from the acid oxalate by containing double the amount of oxalic acid; and, following this nomenclature, it may be called '*quadrurate* of potassa.'

The general formula for the quadrurates—or, as they may be more euphoniously expressed, *quadri-urates*—following the analogy of the quadroxalates, would be:—$H_2(C_5H_2N_4O_3)$, $MH(C_5H_2N_4O_3)$, or—more simply—$H_2\bar{u}$, $MH\bar{u}$.

According to this theory the action of water on the amorphous urate deposit and kindred compounds is to split them up into free uric acid, and bi-urates of the bases contained in them. If this theory be correct, the quantity of uric acid thrown out by water should, of course, exactly equal the quantity retained in solution as bi-urate. With regard to this point, however, Bence Jones's analyses of the potash compound did not come out with the desired exactness. In the first analysis the proportion of uric acid separated by water, as compared with that retained in solution as bi-urate, was not as 1 : 1, as required by the theory, but as 1·27 : 1, and in the second analysis as 1·12 : 1. This discrepancy is considerably greater than could be accounted for by the necessary limits of error in the methods of analysis adopted; and it was impossible to avoid the impression that the proof adduced by Bence Jones of the existence of a true and definite chemical combination corresponding with the hypothetical formula of a quadri-urate was altogether inadequate. These substances, which were

disintegrated by water, might, after all, be only intimate mechanical mixtures of bi-urates with varying quantities of free uric acid—and the action of water upon them might be explained simply as that of a solvent separating a more soluble ingredient from a less soluble ingredient.

Thirty years have elapsed since the publication of Bence Jones's researches. So far as they have had any influence on current views of the pathology of uric acid, they might as well have never been made. For although these researches have received formal mention in works on urinary chemistry, the deductions indicated by them have received no recognition, and have been entirely ignored in the numerous inquiries and discussions which have since taken place on the etiology of uric acid gravel and gout. Until the subject was taken up by myself, no attempt had been made to repeat and verify the observations and experiments. Yet the main suggestion of Bence Jones's investigations, namely, that there existed a third order of uric acid salts, is obviously one of high scientific and practical interest. The cause of this surprising neglect lay probably in the halting and even ambiguous terms in which Bence Jones expressed himself in regard to his results. After giving a clear experimental proof of the disintegrating effects of water on the amorphous urate deposit, he qualifies his statement, without any attempt at explanation, in the following unsatisfactory manner :—

'In other experiments the deposit, when frequently washed with cold water, gave no uric acid crystals at all. Hot water also frequently dissolved only the urates, and caused the whole deposit to pass rapidly through the filter without leaving any uric acid crystals behind.' And in the final summary of his results he writes: 'In

conclusion, then, it appears that the amorphous deposit of urates in the urine has no constant composition. It is a mixture of different acid urates modified in crystalline form by other substances in the urine. . . . Moreover, uric acid is occasionally found in combination with these acid urates, forming quadrurates, and thus rendering the deposit still more liable to vary in its composition.'

Dr. Bence Jones did not return to this subject, though he continued for some years in active scientific work. I can only explain his abandonment of so promising a vein of inquiry on the supposition that he was deterred by the difficulty of obtaining a due supply of material for his experiments. He had to collect the amorphous urate deposit in small parcels at different times and from different sources, as opportunity offered. A supply gathered in this way, of a changeable substance, could not possess the purity and homogeneity necessary for the purposes of quantitative analysis.

In taking up and continuing the investigation thus prematurely dropped by Bence Jones, I was able to reach a point of vantage in regard to these difficulties. I soon learnt that the urinary excretion of the large serpents furnished an abundant source of material which was identical in reactions with the amorphous urate. I also succeeded, by a method to be presently described, in preparing at will from human urine plentiful and fresh supplies of the amorphous urate deposit.

The questions I had to decide were these: Is the amorphous urate deposit, together with the urinary excretion of birds and serpents, a true and definite chemical compound? and does there exist a third order of uric acid salts, differing essentially from the two urates already known, and having a composition corresponding to the hypothetical formula of a quadri-urate? As the main

argument of these lectures rests on the establishment of an affirmative answer to these questions, it is necessary for me to lay before you the experimental evidence on which I rely as sufficing for this purpose.

The materials used in the investigation consisted of: (A) the amorphous urate deposit of human urine; (B) the urinary excretion of birds and serpents—both of these are natural products; and (C) artificially-prepared imitations of these natural products made in the laboratory. Two lines of analysis were pursued in each case. The first was to estimate quantitatively the amounts of the bases and of uric acid in the samples. The second was to proceed by way of what may be termed *Water analysis*, that is to say, to decompose the substance with a large volume of water, and then to estimate respectively the amount of uric acid which was thrown out in the free state, and the amount which went into solution as bi-urate. If the quadri-urate theory be correct, these two amounts should be exactly equal.

I now proceed to lay before you the results of these analyses.

A. *ANALYSES OF THE AMORPHOUS URATE DEPOSIT*

It was found that samples of the amorphous urate deposit obtained from hospital wards or from private patients yielded on analysis results so inconstant that no conclusion with regard to the points under consideration could be drawn from them. In most samples the quantity of uric acid separated by water was larger than that retained in solution, but this excess presented no uniformity of amount. The explanation of this discrepancy lay in the fact, to be more fully noticed in my

next lecture, that the amorphous urate, as it exists in the urine, exists under conditions of change which tend to progressively liberate the uric acid; and as the sediment had to be collected in separate portions from different urines on different days, until a sufficient quantity had been gathered for analysis, it is no wonder that gross variations in its composition were observed. It soon became evident that reliable data could not be obtained from materials collected in this way. This difficulty was, however, surmounted; and I succeeded, by the following process, in obtaining and having always at command an adequate supply of the amorphous urate deposit in a fresh and unchanged state. Healthy urine of medium density is treated with successive additions of bi-carbonate of potash or soda until it becomes slightly alkaline.[1] It is next heated in a flask to the boiling point, and shaken up for a minute or so with excess of pure uric acid. The mixture is now thrown on a filter, and the filtrate is cooled under a running tap of cold water. As cooling proceeds, a dense voluminous precipitate forms, which is an exact counterpart of the natural amorphous urate sediment. The precipitate is separated by filtration, thoroughly washed on the filter with rectified spirit, and dried at blood heat. To obtain a product of uniform composition by this process requires a somewhat nice adjustment of the reaction. If the quantity of alkaline carbonate added be too small, and the alkalescence thereby induced be too faint, the precipitate in cooling is apt to be contaminated with free uric acid. On the other hand, if the alkaline carbonate be added too freely, and the resulting alkalescence be excessive, the precipitate is apt to be contaminated with

[1] A natural alkaline urine, such as is often voided after meals, answers equally well.

bi-urate. These risks are greatly minimised by using the alkaline acetates instead of the alkaline carbonates. The commercial acetate of potash has a slightly alkaline reaction, and it possesses a considerable power of conserving the integrity of the amorphous urate. I obtained a very uniform product by employing normal urine charged with acetate of potash to the extent of 3 per cent. The other steps of the process were the same as those above described. It was observed that if the filtrate was cooled rapidly the resulting precipitate had a finely granular character, just like that of the natural amorphous urate; but if the cooling was allowed to proceed slowly at the temperature of the room, the precipitate fell in larger granules, or in regular spheres with a radiated crystalline structure, resembling closely the spheres of the urinary excretion of birds and serpents.

Samples of amorphous urate deposit prepared in these ways yielded to analysis very constant results. The water analysis was carried out in the following manner. The dried deposit (usually about 0·4 gram) was stirred up in a beaker with 1,000 times its weight of distilled water, and the mixture was slowly heated to about the boiling point until the whole went into solution. The beaker was then set aside. On cooling, the liberated uric acid fell out in large crystals. At the end of forty-eight hours the clear supernatant liquor was nearly all syphoned off; and the remainder, together with the deposited crystals, was thrown on a weighed filter. The crystals were washed very sparingly with cold water and then more freely with rectified spirit. Finally, the filter was dried and weighed. This gave the weight of the uric acid separated by water.[1] The

[1] To get a true result it was necessary to take account of that small portion of liberated uric acid which was still retained in solution after

syphoned-off supernatant liquor, together with the washings from the filter, was then heated to near boiling, and strongly acidulated with hydrochloric acid, and then set aside for forty-eight hours.[1] The precipitated crystals were collected, dried, and weighed, as in the preceding case. When the analyses were conducted in this way, the amount of uric acid separated by water was found to be almost exactly equal to that retained in solution, as is shown in the two following sample experiments :

TABLE I.—*Showing the Results of Water Analysis of two Samples of Amorphous Urate Sediment prepared by the Acetate of Potash Method.*

——	First sample	Second sample
Uric acid separated by water . . .	0·080 gram	0·164 gram
Uric acid dissolved as bi-urate . .	0·077 „	0·159 „

These results agree closely with the requirements of the quadri-urate theory.

A complete quantitative analysis of a sample of amorphous urate sediment obtained by the bi-carbonate of potash method gave the following results; the substance did not contain any lime or magnesia :—

complete precipitation. This was experimentally determined to be, at the usual temperature of the room (60° to 65° F.), 0·0055 gram per 100 cc. This amount was added to the quantity actually found on the weighed filter.

[1] The advantage of adding the acid when the solution is hot, is that the precipitated crystals are much larger, and therefore more easily and perfectly collected, than when the acid is added in the cold. In the atter case the crystals were sometimes so exceedingly minute that it was impossible to avoid serious loss in the processes of filtration and washing.

TABLE II.—*Quantitative Analysis of a Sample of Amorphous Urate Deposit prepared by the Pot. Carb. Process.*[1]

Weight of substance used = 1·328 gram. This yielded :—	
Uric acid	1·113 gram
Potassium	0·065 „
Sodium	0·027 „
Ammonium	0·008 „
Moisture, organic matter, and loss	0·115 „
Total uric acid required to form quadri-urates with the bases present	1·102 „
Total uric acid found	1·113 „

These results agree in the closest manner with the supposition that the deposit was composed entirely and exclusively of quadri-urates of potassium sodium and ammonium.

B. *ANALYSES OF THE URINARY EXCRETION OF BIRDS AND SERPENTS*

1. *Urine of birds.*—During a period of dry summer weather my servant collected for me a quantity of the excreta of a number of fowls kept in a large fowl-run. The pieces were gathered freshly day by day, and were at once dried in the sun on a sheet of paper. When quite dry, the chalk-like stuff encrusting the fæcal masses was carefully chipped off with the point of a penknife and preserved in a stoppered bottle. In this way, in the course

[1] *Mode of Analysis.*—The substance was treated with 50 cc. of water containing 2 cc. strong hydrochloric acid, and allowed to stand 24 hours. The separated uric acid was collected on a weighed filter, washed, dried, and weighed. The filtrate, containing all the bases as chlorides, was evaporated to complete dryness. The residue was taken up with a minimum of water and passed through a filter to separate the small remnant of uric acid mixed with the chlorides. The resultant filtrate was evaporated to a small bulk, and treated with chloride of platinum, and the three bases estimated in the usual way.

of a week, about 4 grams of urinary excrement were obtained in a state of approximate purity. Qualitative testing showed that the substance contained ammonia. On incineration it yielded 8·68 per cent. of a strongly alkaline ash. This ash consisted chiefly of potash and soda, with a small quantity of iron. There were also found in it minute traces of lime and silica, and sulphuric and phosphoric acids. These traces, it was conjectured, were derived from contamination with the sandy materials strewn on the floor of the fowl-run. For this reason the substance was not judged to be sufficiently pure for the purpose of a complete quantitative analysis, but it was perfectly suitable for water analysis. A number of the cleanest-looking pieces were picked out and divided into two parcels of about half a gram each. These were finely powdered, and subjected to water analysis by the method already described. The results are exhibited in the following table :—

TABLE III.—*Water Analysis of Fowls' Urine.*

—	First sample	Second sample
Uric acid separated by water . .	0·160 gram	0·136 gram
Uric acid dissolved as bi-urate . .	0·165 „	0·133 „

It is seen that the results come out with great exactness, in agreement with the requirements of the quadriurate theory.

2. *Urine of serpents.*—The urinary excretion of the large serpents is easily obtained from our Zoological Gardens in massive pieces, quite unmixed with the fæcal discharges and other extraneous impurities. But it is difficult, or even impossible, to obtain the secretion in an absolutely unaltered state, as eliminated by the kidneys.

It is liable, after being voided, to come into contact with the water used for cleansing the cages in which the creatures are confined; and water, as we have seen, speedily disintegrates it. Again, if the substance be not at once completely dried on the hot-water bath, it undergoes bacterial decomposition, and is thereby transformed into bi-urate of ammonia. This is the condition in which 'serpents' urine' as supplied by the dealers is generally found. But even if both these sources of change are avoided by taking proper precautions, there is yet another which no care can obviate. The large serpents void their urine at long intervals, varying from a week or ten days to six or seven weeks. During this long sojourn in the urinary passages, the secretion undergoes slow changes which affect its chemical constitution. I have always found serpents' urine, when examined in the fresh state, to have a sharply acid reaction. Under these conditions a certain amount of decomposition of the urates, with liberation of free uric acid, is inevitable.[1] Accordingly, when samples of serpents' urine were subjected to water analysis, however carefully the samples had been collected and preserved, the amount of uric acid separated by water was always found to be considerably in excess of that which went into solution as bi-urate. The invariable presence in the secretion of free uric acid was thus demonstrated. The subjoined table exhibits some of the results obtained by water analysis of freshly gathered specimens of the urinary excrement of the boa :—

[1] Herein, no doubt, lies the remarkable difference in the results of water analysis of the urine of the fowl and that of the boa. The fowl discharges its urine many times a day. There is no detention of it in the urinary passages, and therefore no time for the occurrence of appreciable secondary changes.

TABLE IV.—*Water Analysis of Four Samples of Serpents' Urine.*

——	I.	II.	III.	IV.
	gram	gram	gram	gram
Uric acid separated by water	0·128	0·110	0·204	0·215
Uric acid dissolved as bi-urate	0·117	0·085	0·141	0·140

It is seen that in each experiment the quantity of uric acid separated by water was in excess of that which went into solution as bi-urate, and that, moreover, the proportion of this excess bore no constant relation in the several samples. The urine of the serpent when at length voided would thus appear to consist of quadri-urates contaminated with a variable admixture of free uric acid.

The explanation above offered to account for the discrepant results obtained by water analysis of serpents' urine would, however, not apply to a quantitative estimation of the uric acid and the bases found in the excretion. For, although the changes indicated as occurring during the lengthened sojourn of the secretion in the urinary passages would produce a partial displacement of the relations between the uric acid and its attached bases, the quantities of these would remain unaltered, and they would still form in their due proportions part and parcel of the semi-solid excrement as finally voided. The following quantitative analysis of a massive and very pure specimen of the urine of the boa justifies the correctness of this explanation. The material used for the analysis was taken exclusively from the interior portions of the mass.

TABLE V.—*Complete Quantitative Analysis of the Urine of the Boa.*

Ten grams yielded :—		
Uric acid	8·280	grams
Potassium	0·333	„
Sodium	0·106	„
Ammonium	0·192	„
Moisture, organic matter, and iron—with traces of lime—and loss	1·089	„
	10·000	„
Uric acid combined as quadri-urate with the bases present	8·071	„
Free uric acid	0·209	„

The results of this analysis came out closely in accordance with the requirements of the quadri-urate hypothesis. The quantity of uric acid over and above that required to form quadri-urates with the bases present, and which might be regarded as existing in the free state, did not exceed 2·5 per cent. of the total uric acid found.

C. *ANALYSES OF ARTIFICIALLY-PREPARED QUADRI-URATES*

As already stated, Bence Jones succeeded in preparing compounds of uric acid with potassium and sodium which were decomposable by water, by adding acetic acid to cold solutions of uric acid in potash or soda ley until a precipitate was produced. This method was, however, found to give very uncertain results. If the acetic acid was added a little too freely, the precipitate was contaminated with free uric acid; and, on the contrary, if too little acetic acid was added, the precipitate was contaminated with bi-urate; it was almost impossible to hit the mark with precision. The following

process was found to yield much more uniform results. 300 cc. of a 3 per cent. solution of acetate of potash were heated to boiling in a flask, and then shaken up with two grams of uric acid for about a minute. The mixture was filtered hot, and the filtrate rapidly cooled under a running tap of cold water. A dense voluminous precipitate formed. This was thrown on a filter, and washed first with rectified spirit, and then thoroughly with absolute alcohol, and finally dried at blood heat. The substance thus obtained had a coarsely granular appearance under the microscope, and it was rapidly decomposed when treated with water. If the cooling was allowed to take place more slowly in the warm chamber, or even at the temperature of a warm sitting-room, the precipitate fell down in regular spheres, possessing a radiated crystalline structure, resembling very closely both in size and appearance the spheres of the birds' and serpents' urine.

The following table exhibits the results of analysis of this compound :—

TABLE VI.—*Water Analysis and Quantitative Analysis of a Sample of Potassium Quadri-urate prepared by the Acetate of Potash Method.*

Water analysis :—

Uric acid separated by water . . .	0·84 gram
Uric acid dissolved as bi-urate . . .	0·85 ,,

Quantitative analysis		Proportions per cent.	
		Found	Calculated
Uric acid .	0·198 gram . .	89·75	89·60
potassium .	0·0226 ,, . .	10·25	10·40

The numbers in both these analyses of the potassium compound come out with almost perfect exactness in

agreement with the quadri-urate theory of its composition.

The corresponding sodium compound was prepared by shaking up one gram of uric acid with 100 cc. of a boiling hot 5 per cent. solution of acetate of soda, filtering hot, cooling the filtrate rapidly on ice, collecting the resultant precipitate at once on a filter, washing with absolute alcohol, and drying at blood heat. The operations have to be carried out as rapidly as possible, otherwise free uric acid is thrown out. Analysis of the sodium compound thus prepared yielded the following results:—

TABLE VII.—*Quantitative Analysis of a Sample of Sodium Quadri-urate prepared by the Acetate of Soda Process.*

—	Proportions per cent.	
	Found	Calculated
Uric acid . 0·329 gram . .	94·00	93·58
Sodium . . 0·021 ,, . .	6·00	6·42

Here, again, the quantities of uric acid and sodium found agree closely with the calculated amounts required to form a quadri-urate.

The series of analyses just detailed furnish an adequate proof that the compound of uric acid which is decomposable by water is no mere mechanical mixture, but is a true and definite chemical combination, having a centesimal composition corresponding to that of a hypothetical quadri-urate, with the general formula $H_2\bar{U}, MH\bar{U}$. In deference to the authority of Bence Jones I propose to adhere to the designation quadri-urate, without, however, prejudging the question whether in reality

the analogy with quadroxalate be a chemically sound one.[1]

It now only remains to trace the source of the discrepancies which occurred in the analyses of Scherer and Bence Jones, and which also were encountered by myself. It frequently happened in the course of my experiments that a precipitate having a granular amorphous character, and freely decomposable by water, did not yield, when subjected to water analysis, the required quantitative results. The amount of free uric acid separated by water was either too large or too small as compared with that retained in solution as bi-urate; and these discrepancies were not infrequently obviously greater than could be accounted for by any errors in the analytical procedures. The explanation of these unconformable results is, I believe, to be found in the fact that the quadri-urates, during the act of precipitation,

[1] In addition to the quadri-urates of potassium and sodium above described, I succeeded in preparing quadri-urates of ammonium, calcium, and magnesium by the following methods:—

Ammonium quadri-urate was prepared by boiling a gram of uric acid with 200 cc. of 1 per cent. dilution of the strong liquor ammoniæ. The solution was filtered hot, and then rapidly cooled on ice. Through the cold liquid an abundant stream of carbonic acid was passed until a bulky precipitate was produced. This was at once filtered off, quickly washed with alcohol, and dried. The whole process must be carried on rapidly, otherwise the quadri-urate passes into bi-urate. *Calcium quadri-urate* was prepared by dissolving half a gram of uric acid in 100 cc. of cold lime water. To the filtered solution acetic acid was added drop by drop until neutralisation was approached. An abundant precipitate was then thrown down, which was caught on a filter, washed with rectified spirit, and dried. *Magnesium quadri-urate* was prepared by digesting uric acid and calcined magnesia, both in excess, with distilled water at blood heat, with frequent agitation, for about ten minutes. The mixture was filtered warm, and the filtrate rapidly cooled under a running tap of cold water. A dense flocculent precipitate formed, which was quickly washed with alcohol and dried.

are liable to acquire a contamination of free uric acid, or of bi-urate, in an amorphous state. If the medium from which the quadri-urate is precipitated contains free uric acid in solution, as must usually, if not always, be the case with acid urines, the precipitated quadri-urate will mechanically carry down with it a certain amount of free uric acid; on the other hand, if the medium be alkaline, and contain bi-urate in solution, as must usually occur in the artificial preparation of quadri-urates, the precipitate will carry down with it a certain admixture of bi-urate. The following experiment, among others, appears to substantiate this conjecture. 500 cc. of an acid urine were divided into two equal portions, A and B. Sodium bi-carbonate was added to A in the proportion of 0·1 per cent. This addition produced only a feeble degree of alkalescence. The urine was then heated to boiling and shaken up with one gram of uric acid. The mixture was now found to be slightly acid. After filtration it was rapidly cooled under a running tap of cold water. The resulting precipitate was filtered off, washed with rectified spirit, and dried. This yielded to water analysis:—

Uric acid separated by water . . .	0·164 gram
Uric acid dissolved as bi-urate . . .	0·142 „

The other portion, B, was treated with sodium bi-carbonate in the proportion of 0·2 per cent. This addition rendered the urine freely alkaline. B was then treated exactly like A. The resulting precipitate gave with water analysis:—

Uric acid separated by water . . .	0·159 gram
Uric acid dissolved as bi-urate . . .	0·174 „

In both cases the precipitate, when examined under the microscope, was found to be wholly amorphous; that

from A did not show any crystals of uric acid, and that from B did not contain any crystals of bi-urate. These results are only explicable on the supposition that in the one case the quadri-urate was contaminated with free uric acid, and in the other with bi-urate, in an amorphous condition.

GENERAL CHARACTERS AND REACTIONS OF THE QUADRI-URATES

The quadri-urates present themselves usually as amorphous powders; but the spheres of birds' and serpents' urine are distinctly crystalline, and display a black cross when examined with polarised light. These forms are permanent in the air if kept perfectly dry. They readily assume a gelatinous modification,[1] and when examined under the microscope in this state appear as large translucent globules. The quadri-urates are difficult to obtain in a state of chemical purity; they are apt, when produced artificially, to be mixed either with free uric acid or with bi-urate—and, when obtained from the urine, to be contaminated with pigment or with traces of extraneous saline matters. They cannot be dissolved unchanged in any simple menstruum. They are insoluble in absolute alcohol, ether, glycerine, chloroform, and the volatile and essential oils. When treated with hot water the quadri-urates first pass into solution in their integrity; but this integrity is only maintained for a brief moment, and they forthwith disintegrate into free uric acid and bi-urate. It is, therefore, impossible to purify them, as most other substances are purified, by repeated solution and re-precipitation. They are

[1] See Lecture III., where an account is given of the gelatinous modifications of the bi-urates and quadri-urates.

extremely unstable, and they tend to change in two opposite directions. In weak solutions of the alkaline carbonates or of the di-metallic phosphates they slowly take up an additional atom of base and are converted into bi-urates. On the other hand, in water, and in watery solutions of the neutral salts, they are split up into free uric acid and bi-urate. These two reactions cover the behaviour of the quadri-urates in the blood and the urine respectively, and furnish a key to the chemical processes which culminate in the formation of gouty deposits and calculous concretions, as will be hereafter more fully explained.

The only appropriate solvent for the quadri-urates is healthy urine. In acid urines they dissolve freely with the aid of heat, and are again precipitated unchanged on cooling. Such solutions are, however, not quite stable; after a time their uric acid is slowly, and, at length, completely, liberated. The quadri-urates are still more freely soluble in hot alkaline urines, and in these media they continue permanently unaltered if guarded against septic changes. When such solutions are made at boiling heat, and are saturated, they throw down on cooling bulky deposits which are identical in appearance and reactions with the natural amorphous urate sediment.

Recapitulation.—The subjoined paragraphs exhibit in a concise form the principal conclusions arrived at concerning the occurrence in the body of free uric acid and of the three urates, in the physiological and in the pathological state. Some of the statements here made must be taken for the present on trust; the evidence on which they are based will be adduced hereafter.

1. *Free uric acid*—$H_2\breve{U}$.—Not known physiologically, neither in the body nor in the urine. Known clinically

and pathologically as crystalline sediments in the urine, and as gravel and calculus in the urinary passages.

2. *Neutral urates*—$M_2\bar{u}$.—Not known physiologically nor pathologically. Only known as laboratory products.

3. *Bi-urates*—$MH\bar{u}$.—Known pathologically as components of gouty concretions in the tissues. Known in the urine only after the secretion has undergone ammoniacal fermentation. It is doubtful if they ever exist physiologically in the blood or tissues.

4. *Quadri-urates*—$H_2\bar{u}$, $MH\bar{u}$.—These are specially the physiological combinations of uric acid. They exist normally in the urine and probably also in the blood. They constitute the entirety of the urinary excretion of birds and serpents; all the morbid phenomena due to uric acid arise probably from secondary changes in the quadri-urates.

COMPARATIVE PHYSIOLOGY OF URIC ACID, AND THE EVOLUTION OF MAMMALIAN URINE

The study of the amorphous urate deposit, and of the urinary excretion of birds and land reptiles, suggests some interesting reflections. We have seen that the amorphous urate deposit is substantially the same thing as the solid or semi-solid urine of birds and serpents; all these consist of the quadri-urates of potassium, sodium, and ammonium. But whereas in the urine of man and mammalia the quadri-urates are, from a physiological point of view, only an insignificant item amid a host of other more important ingredients, the quadri-urates constitute practically the whole of the renal excretion of birds and serpents. The urine of these creatures may be said to be exclusively composed of a substance identical with the amorphous urate

sediment of human urine; or, to put it in another way, the amorphous urate is the physiological homologue of the entire renal activity of birds and serpents. The kidneys of birds and serpents are anatomically composed of the same structures as the mammalian kidneys; they are provided with the same kinds of secreting tubes and epithelial elements, the same curious Malpighian tufts and capsules, and yet how widely different is the product of their functional activity! It is not merely that there is a substitution of uric acid for urea as the final term of nitrogenous metabolism, but there is also the strongly contrasted simplicity of the urine of birds and serpents with the complexity of mammalian urine. In birds and serpents the renal function is presented to us in its primitive simplicity. In these creatures the kidneys perform one single and simple physiological act, namely, the elimination of nitrogen as uric acid. For, although the uric acid is excreted in union with bases, the quantity of these bases is the absolute minimum requisite to bring uric acid into a state of chemical combination, and thereby to deprive it of that strong crystalline character which otherwise would make its passage along the delicate exit tubules of the kidney a physical impossibility. The chlorides, phosphates, and sulphates, the lime and magnesia salts, the pigments, and the large volume of water—all of which figure as prominent and even essential components of mammalian urine—are either wholly absent from the urine of birds and serpents, or are only present in such minute traces as might be derived from the lubricating mucus and epithelial débris with which the secretion is incidentally admixed.

It would be interesting to trace the successive steps along which the evolution of the complex mammalian urine took place from this simple beginning. We are

familiar with much that has been said and written of mammalian descent from simpler types. The eyes and thoughts of biologists have, however, been chiefly fixed on the anatomical evolution. But there is assuredly also such a thing as functional evolution. The anatomical evolution of the kidneys seems to have reached its term in the lowest vertebrate forms; the mammalian kidney presents structurally no essential advance on that of birds and serpents; but an immense functional evolution has taken place, and an examination of its progress through the tribes of fishes, amphibia, marsupials, and the lower mammals, up to man, would prove an instructive biological study. The results of such a study would probably show that the evolution of mammalian urine turned mainly on the point that the mammalian plan required that the renal excretion should be voided, not in the solid or semi-solid form, but in the liquid form, as a watery solution. This modification would at once necessitate the discarding of uric acid as a vehicle for the elimination of nitrogen. Uric acid and its compounds are strongly characterised by sparing solubility; and on no terms, compatible with the conditions prevailing in the animal economy, could the requisite quantity of uric acid be got into solution in a watery urine. Urea, on the contrary, is an extremely soluble substance. In regard to the prime function of the kidney, therefore, Nature solved the problem easily by substituting urea for uric acid. But why was not the problem solved completely—why was there left in mammalian urine this small, and apparently purposeless, but to man very mischievous, residuum of uric acid? No satisfactory answer can at present be given to this question. It seems not impossible that the explanation lies in the fact that the mammalian type—the most

recently evolved of the vertebrate types—has not yet, in this particular, reached its ideal perfection. A good deal may, I think, be said in favour of this conjecture.

The occurrence and proportion of uric acid in the urine of the various tribes of mammalia is remarkably inconstant. Meissner[1] states that the urine of the carnivora does not always contain uric acid; in the urine of dogs and cats it was repeatedly found to be altogether absent. According to the same authority, uric acid is only found regularly in the urine of these animals when fed on flesh and in the fasting state; it disappears when they are fed on food poor in albuminoid matters. Stadthagen[2] found that in the urine of dogs fed on flesh the proportion of uric acid to urea ranged between 1 to 280 and 1 to 800. In the urine of rabbits uric acid is sometimes present and sometimes absent. Salomon found it always present in the urine of the pig, but only in small quantity; and its proportion to urea was only in the ratio of 1 to 150. In the case of man the quantity of uric acid excreted presents great individual variations both in regard to its absolute quantity and in regard to its proportion to urea. The ratio of uric acid to urea in human urine appears to range between 1 to 30 and 1 to 50, and the ratio, according to Marès, is special for each individual. Dr. Haig estimates this ratio as 1 to 33; and he regards any deviation in the direction of plus or minus from this ratio as due either to temporary retention of uric acid in the body or to elimination of previously retained uric acid.

If we look broadly at the renal function throughout the animal series, we see that, in essence, it consists in a provision for the elimination of waste nitrogen. This

[1] *Zeitschrift f. rat. Med.* (3) Bd. 24, p. 104; Bd. 31, p. 306.
[2] *Virchow's Archiv*, Bd. 109, p. 418.

is a function of capital importance and necessity in the nutrition of animals, comparable to the excretion of carbon by the lungs; and according to all physiological analogies it must be at bottom one and the same throughout the Animal Kingdom. Starting from the highly complex albuminoid molecule, and descending by a train of intermediate steps, the histolytic process ends in some comparatively simple crystalline azotised body. The precise nature of the final term in the histolytic transformation is apparently of small significance, and seems to depend on what may be described as the general convenience of the economy. It may be urea, uric acid, hippuric acid, or guanin, or a mixture of all these. And it is reasonable to assume that all these bodies are physiologically homologous, and that their broad physiological relations are identical. What urea is to the mammal, uric acid is to the bird and serpent; what urea is to man, urea with hippuric acid is to the horse and ox. The office of the kidneys is to separate the final term of proteid metabolism, whatever that final term may be.

These considerations point to the idea that the residuum of uric acid in mammalian urine may be something in the nature of a vestigial feature— something analogous with the vermiform appendix, the ductus arteriosus, or the ear-point. These rudimentary structures are now regarded by biologists as indications of the line of ontological descent. On this view the presence of uric acid in the mammal's urine should be regarded as a 'Memory' of some ancestral form, which eliminated its nitrogen as uric acid. The extreme inconstancy of uric acid, both in regard to its presence and proportion in the urine of different species and in different individuals of the same species, agrees perfectly with this

theory; for vestigial structures are especially remarkable for their inconstancy. Such structures also, like uric acid, although impotent for good, are sometimes powerful for evil. This speculation will be again adverted to in my fourth lecture in connection with the genesis of the gouty diathesis.

LECTURE II

ON THE CHEMISTRY OF URIC ACID GRAVEL —PROPHYLACTIC TREATMENT

Mr. President and Gentlemen,—In the preceding lecture I laid before you an account of those points in the chemistry of uric acid and the urates which seemed to have a bearing on the subject-matter of these lectures. I showed that there were three orders of uric acid salts; that in addition to the neutral urates and bi-urates which had long been recognised, there existed a third order, namely the quadri-urates, which, in reactions and chemical constitution, differed widely from the other two. It was pointed out that the neutral urates, from their mode of origin and reactions, could not, with our present knowledge, be regarded as having any possible concern in the vital history of uric acid. It was also pointed out that the bi-urates, although known to us pathologically as constituents of gouty concretions, were not really known to us with certainty as physiological constituents, neither of the blood nor of the urine. On the other hand, it was shown that the quadri-urates existed normally in human urine, and in the urine of birds and serpents; and it will be demonstrated later on that when uric acid is brought into relation with the bodily fluids —with the blood, lymph, and synovia—it enters into solution in the first instance, not as neutral urate nor as bi-urate, but as quadri-urate. From all these con-

siderations it would appear that whenever and wherever uric acid exists in the healthy body it exists exclusively as a quadri-urate. The quadri-urates may, therefore, be regarded as being in a special sense the physiological salts of uric acid, and as constituting the only form in which uric acid subsists in the living body in the normal state. It may, moreover, be further inferred, that when uric acid gives trouble, and originates morbid phenomena, the mischief arises proximately from the uric acid departing, in one direction or another, from this normal state of combination.

I now proceed to consider more particularly the state of uric acid in human urine; the conditions which surround it, and the factors which tend to determine its precipitation, or to prevent its precipitation, in that fluid.

INHERENT TENDENCY OF URINE TO THE SPONTANEOUS LIBERATION AND PRECIPITATION OF ITS URIC ACID

The chemical reactions and physical conditions which are concerned in the production of uric acid concretions are both varied and complex. Uric acid exists in the urine in combination with the alkaline bases, with potash, soda, and ammonia. In perfect health these combinations maintain their integrity, not only while the urine is detained in the urinary channels, but even for some considerable time after it has been discharged. This, however, is not always the case. In certain contingencies these combinations are prematurely decomposed —their uric acid is set free, and, owing to its sparing solubility, is precipitated from the urine in the crystalline form. In calculous subjects this event may take place in the kidneys or bladder and give rise to the incidents of gravel. In less urgent instances the

precipitation takes place soon after the urine is voided, in the form of copious urinary deposits. But apart from these pathological cases, and cases which hover on the pathological border-land, it may be shown that perfectly normal urines betray the same tendency. A considerable series of observations on this point were made on the urines of persons who were entirely free from any proclivity to calculous disorders. It was found that all acid urines, if they were guarded against septic changes,[1] invariably deposited uric acid sooner or later; except, of course, when the proportion of that substance was so small that the volume of urine was sufficient to hold it in solution after it had all attained to the free state. The time of the occurrence of the precipitation varied greatly. It usually began within twenty-four hours after the urine was voided, sometimes in a day or two, and sometimes it was delayed for a week or even longer. The duration of the process varied with the earliness or lateness of its onset. Speaking roughly, urines which began to deposit uric acid in a few hours, completed the process in a few hours longer; but if the onset was delayed for some days, the deposition of crystals went on for some days subsequently. When the process was at length completed—whether that was early or late—all the uric acid had disappeared from solution; the filtered supernatant urine gave not the

[1] This was usually effected by adding a few drops of chloroform to the test-tubes or phials in which the urines were kept. Sterilisation by heat is not applicable in these experiments, because the reaction of the urine is thereby modified. It was found that acid urines became less acid when they were subjected to the heat of boiling water, even when the urines were enclosed in hermetically-sealed tubes; and if the heat was continued for thirty or forty minutes, the reaction changed from acid to alkaline. This change is due to decompositions of urea; for, as has long been known, urea in watery solutions undergoes with continued heating a gradual transformation into carbonate of ammonia.

slightest precipitate with hydrochloric acid, nor could there be detected in it, on evaporation to a small bulk and with careful search, any trace of uric acid. This was, at least, the result arrived at with urines of medium density in which free precipitation had taken place.[1] The precipitation took place with equal certainty whether the urine was kept in the warm chamber at blood heat, or was kept at the temperature of the air. In the latter case the urine sometimes threw down a deposit of the amorphous urates. By this occurrence the urates were in some degree withdrawn from the operation of the disintegrating forces; but this only caused delay. Ultimately the deposit changed entirely into crystals of uric acid.

We must, therefore, recognise in normal acid urines an inherent tendency to the liberation and precipitation of their uric acid. This tendency only assumes a morbid significance when the event occurs prematurely, while the urine is still sojourning in the kidneys or bladder. Viewed in this light, pathological gravel may be regarded as due to an exaggeration of conditions which prevail, in a less pronounced degree, in the normal state; and an elucidation of these conditions may be reasonably expected to throw a light on the etiology of gravel and calculus, and perhaps furnish hints which may be turned to therapeutical uses.

CHEMICAL EXPLANATION OF THE SPONTANEOUS PRECIPITATION OF URIC ACID IN URINE

The chemical reactions which are concerned in the spontaneous precipitation of uric acid in acid urines are

[1] I do not suppose that the urines in these cases were really absolutely free from uric acid. Minute traces of uric acid are difficult to detect in urine, and especially in high-coloured urines.

very interesting to trace out. It may be proved that uric acid always subsists in the unchanged urine as a quadri-urate. It has already been shown that the amorphous urate sediment has this composition. It may also be demonstrated that the same compound exists in a state of solution in clear non-sedimentary urines. When such urines, whether they be acid or alkaline, are concentrated to a small bulk on the water-bath, and filtered hot, and then cooled on ice, a dense precipitate is thrown down. When the precipitate is collected on a filter and well washed with rectified spirit, it is found to possess the properties of a quadri-urate—it is granular in character and is decomposable by water, with free emission of uric acid crystals. Besides, the only other combination of uric acid which could conceivably be present in urine is the bi-urate; and I shall presently prove to you that the bi-urate cannot maintain its integrity in normal urine, but is forthwith transformed into quadri-urate.

We may, therefore, conclude without any misgiving that the quadri-urate is the form, and the only form, in which uric acid exists in normal urine, and may draw the inference that when uric acid makes its appearance therein in any other guise, that event is due to secondary changes in the quadri-urate.

Let us now consider the medium, the urine, in which the quadri-urate is dissolved. The urine is a watery solution, which, besides urea and extractives, contains a number of mineral salts. Among these salts the most important, in regard to the point under consideration, are the alkaline phosphates. These regulate, in the main at least, the reaction of the urine. The phosphates easily oscillate between the mono-metallic forms or superphosphates, which have an acid reaction, and the

di-metallic forms, which have an alkaline reaction. When the former preponderate, as is usually the case, the urine is acid; when the latter preponderate, the urine is alkaline.

We have, therefore, in an acid urine, the quadri-urate existing in the presence of water and of super-phosphates. These conditions ensure the ultimate complete liberation of the uric acid. The first step in the process is the splitting up of the quadri-urate by the action of the water of the urine into free uric acid and bi-urate. By this reaction half the uric acid is set free. But the bi-urate resulting from this reaction is immediately retransformed in the presence of superphosphate, by a double decomposition, into quadri-urate. Two atoms of bi-urate with one atom of superphosphate (mono-metallic phosphate) change into one atom of quadri-urate and one atom of di-metallic phosphate, according to the subjoined equation :—

$$\underset{\text{Bi-urate}}{2(MH\bar{u})} + \underset{\substack{\text{Mono-metallic}\\ \text{phosphate}}}{(MH_2PO_4)} = \underset{\text{Quadri-urate}}{(H_2\bar{u},MH\bar{u})} + \underset{\substack{\text{Di-metallic}\\ \text{phosphate.}}}{(M_2HPO_4)}$$

These alternating reactions—breaking up of quadri-urate by water into bi-urate and free uric acid, and re-composition of quadri-urate by double decomposition of bi-urate with mono-metallic phosphate—go on progressively until all the uric acid is set free.

That these are the actual steps of the process whereby the totality of the uric acid is eventually liberated in acid urines, may be deduced from the following considerations and experiments. The first step—the breaking up of the quadri-urate into free uric acid and bi-urate by the action of the water of the urine—is in accord with what has been already shown to be the reaction of water with quadri-urates. The occurrence of

the second step—the transformation of bi-urate in the presence of superphosphate into quadri-urate—is directly established by the following experiments.

A saturated solution of potassium or sodium bi-urate is made in hot water and then allowed to cool. When to this solution a strong solution of one of the alkaline superphosphates is added drop by drop, a dense white precipitate is thrown down, which, on examination, is found to possess the characteristic reactions of the quadri-urates. A similar result is obtained when the experiment is repeated with an acid urine instead of a solution of superphosphates. If the bi-urate solution is mixed with about one-third of its bulk of an acid urine of medium density, a copious precipitate forms. This precipitate has the usual characters and reactions of the amorphous urate deposit or quadri-urates. That the result in this latter case is not due to the precipitation of quadri-urate pre-existing in the urine is proved by repeating the experiment with the same urine after it has been deprived of its uric acid by repeated filtration through uric acid ;[1] it still throws down amorphous urate abundantly with the bi-urate solution.[2]

[1] It is a curious fact that acid urines are entirely deprived of their uric acid by passing them three or four times through a filter on which a little heap of six or eight grains of pure uric acid has been placed. This result is, I believe, brought about in the same way as the spontaneous precipitation of uric acid in acid urines, as already explained ; but the process is greatly accelerated by the superadded force of crystalline aggregation. I have given an account of this matter, in a paper ' On Pfeiffer's Test for Latent Gout,' in the *Lancet* for January 4, 1890.

[2] The transformation of bi-urate into quadri-urate takes place even in alkaline (not ammoniacal) urines. This was proved by adding a solution of potassium bi-urate to a urine which had first been deprived of its uric acid by being passed repeatedly through the uric acid filter, and then rendered slightly alkaline by the addition of di-metallic phosphate or bicarbonate. A urine so treated, when evaporated to a small

The transformation of bi-urate into quadri-urate in the presence of superphosphate explains why true bi-urates never appear as a deposit in normal and undecomposed urine. It also explains why in the spontaneous precipitation of uric acid in urine the process goes on, not merely until a moiety, but until the whole of the uric acid is set free and deposited.

THE INGREDIENTS WHICH RETARD THE DECOMPOSITION OF THE QUADRI-URATES IN NORMAL URINE

It has just been shown that uric acid exists in the urine in the form of quadri-urate, and that when the urine is secreted with an acid reaction—that is to say, for some sixteen or twenty hours out of the twenty-four—this compound exists amid conditions which, if they stood alone and uncontrolled, would lead to speedy precipitation of uric acid in the free state. But in the normal course no such early precipitation occurs; it only occurs as a remote and postponed event, after the urine has been voided. It is obvious, therefore, that the urine contains certain ingredients which inhibit, or greatly retard, the water of it from breaking up the quadri-urates. Were it not for the presence of these inhibitory ingredients, uric acid would be thrown out daily in the urinary passages—and everyone would be

bulk, and then cooled, threw down a dense amorphous precipitate, which possessed the properties of quadri-urate, and was decomposable by water. This result seems to indicate that the transformation of bi-urate into quadri-urate in the urine may take place in other ways than that above described. For example, two atoms of bi-urate with one atom of di-metallic phosphate might change into one atom of quadri-urate and one atom of tri-metallic (or basic) phosphate; or two atoms of bi-urate with one atom of bicarbonate might similarly change into one atom of quadri-urate and one atom of mono-carbonate. The reaction would be perfectly parallel in all these cases, although, of course, not identical.

subject to gravel. Hence an inquiry into the nature of these inhibitory agents has a pathological as well as a physiological interest, and bears directly on the etiology of calculous disorders. The inquiry is not a simple one. The urine is a very complex fluid. It contains, besides urea, a number of saline constituents, together with pigmentary and other extractives. Where, among all these, are the inhibitory agents to be found?

Attention was first directed to the *saline constituents*. It was found that when urine was dialysed, whereby its crystalline ingredients were for the most part removed, it lost to a considerable extent its power of retarding the decomposition of the quadri-urates. This observation indicated that the inhibitory power resided, partly at least, in the crystalloids of the urine. The chief crystalloids of the urine are urea and the chlorides, phosphates, and sulphates of potash, soda, ammonia, lime, and magnesia. Solutions of these several substances in distilled water were prepared, and their effect on the quadri-urate was tested in the following manner. A speck of a purified specimen of the amorphous urate deposit was placed on a glass slide, and intimately mixed with a drop of the solution to be tested. The covering-glass was then applied and the result watched under the microscope. The time at which crystals of uric acid began to make their appearance was taken as a measure of the activity of the tested solution in decomposing the quadri-urate. The standard of comparison was distilled water, which usually caused crystals to appear in five minutes. Solutions of urea of various strength acted precisely with the same speed as distilled water. It was obvious that urea had no share in the power resident in urine of retarding the decomposition of the quadri-urate. The chlorides and sulphates, in the proportion of 1 per cent. and

upwards, imparted to water a considerable power of delaying the appearance of crystals. The potash salts were found to have more effect in this respect than the corresponding salts of ammonia and soda. The common disodic phosphate (rendered perfectly neutral to test-paper by the addition of phosphoric acid) showed about the same inhibitory power as sodium chloride. None of these solutions, nor any mixture of them, approached the natural urine in power of postponing the decomposition of the amorphous urate. More pronounced effects were obtained with the dipotassic phosphate. A solution of this salt, containing only 0·2 per cent., and perfectly neutralised, appeared to act almost as slowly on the deposit as a normal acid urine. Urines which were alkaline from fixed alkali had absolutely no disintegrating effect on the amorphous urate.

Attention was next turned to the *colouring matters* of the urine. The amorphous urates have an intense affinity for urinary pigment; the pigment cannot be removed from them by any solvent which does not, at the same time, destroy their integrity. I had noticed that deeply-tinted urates were more slowly decomposed by water than pale-coloured urates. It had also been noticed that artificially-prepared quadri-urates, and the quadri-urates which constitute the urinary secretion of birds and serpents, all of which are devoid of colouring matters, are much more quickly broken up by water than the natural amorphous urate, which is always more or less tinted. Moreover, it was found that a urine which had been filtered through animal charcoal, and thus deprived of its pigment, acted very much more rapidly on the amorphous urate deposit than the same urine before it had been filtered through charcoal.

It can, therefore, scarcely be doubted that the pig-

ments of the urine play an important part among the ingredients which impart to normal urine its remarkable power of retarding the decomposition of the amorphous urate. In the febrile state, and in other wasting disorders, the urine is sharply acid and rich in urates; and yet such urines are not prone to deposit free uric acid, though very prone to deposit amorphous urates. In these cases the urine is always deeply coloured, and the pigments are probably the chief agents which prevent the precipitation of free uric acid under these circumstances.

These observations do not, I think, exhaust this part of the inquiry. It is not improbable that, besides the salts and pigments, there are other components of the urine which contribute to retard the liberation of its uric acid. Moreover, urinary pigments are of several kinds, and they may not all be alike in regard to their power of protecting the integrity of the quadri-urates.

CHEMICAL ETIOLOGY OF URIC ACID GRAVEL

The more remote and predisposing causes of gravel do not come within the scope of the present inquiry. Whatever these causes may be, they must be translated into changes in the composition of the urine before they can determine the occurrence of calculous accidents. No amount of morbid proclivity to uric acid gravel can take effect if the urine be alkaline, nor if the proportion of uric acid in it fall below a certain point. The causes which will be here considered are those which lie exclusively in the chemical constitution of the urine itself.

I have just given proof that the salines and pigments of the urine exercise a protective influence against premature precipitation of uric acid; and it may hence be

inferred that a diminution of these salines and pigments may sometimes act, in a negative manner, as a determining factor in the production of gravel and stone.

Poverty of the urine in saline matters.—This is probably an influential factor in the disproportionate frequency of stone among the children of the poor, as compared with the children of the easier classes.[1] The prevalence of stone among the natives of India is also probably to be explained in the same way. The children of the poor are fed largely on farinaceous articles—bread, gruel, oatmeal and potatoes—with but a scanty allowance of milk, meat, and fish. Wheat-flour contains only 0·51 per cent. of mineral matter in proportion to the totality of the dry substance—oatmeal only 2·50 per cent.—potatoes only 2·50 per cent.; whereas milk contains 5·50 per cent. and the various forms of meat and fish 5 to 5·50 per cent. Rice, which forms so large a part of the diet of the natives of India, only contains 0·39 per cent. of mineral matter in proportion to the totality of the dry substance of the grain. These enormous differences in the amount of saline ingredients in the articles of food must, of course, make a corresponding difference in the proportion of the saline constituents of the urine—because saline matters pass out of the body almost exclusively through the kidneys. On the other hand, the well-known immunity enjoyed by sailors from stone and gravel depends, no doubt, as Mr. Plowright has shown, on the prodigious quantity of salt which seafaring men habitually consume with their food. The same observer has pointed out that the dwellers in a district of Norfolk called Marshland,

[1] The rarity of stone among the children of the rich and its comparative frequency among the children of the poor is a well-attested fact. See on this point Sir Henry Thompson's *Clinical Lectures on Diseases of the Urinary Organs*, 8th Ed. p. 196.

where the drinking-water is brackish, are singularly free from stone, as compared with their less fortunate neighbours in the adjacent districts of that county.[1]

Deficiency of pigment in the urine.—In chronic Bright's disease, with contracting kidneys, the urine is conspicuously pale, and is often, indeed, almost entirely devoid of pigment. There is no excess, but rather a diminution of uric acid in the urine in these cases; nevertheless, deposits of uric acid are by no means uncommon, and sometimes actual renal gravel occurs. The percentage of salines is also low, and this doubtless contributes to the result; but probably the prepotent factor in the precipitation of uric acid in these cases is the deficiency of pigment in the urine.

Poverty of the urine in salines and pigments, however, only accounts for certain limited groups of calculous cases. There are other and larger groups in which the urine is neither defective in salts nor in colouring matters. The subjects of calculous disorders among the easy classes—especially those of a gouty type—usually void a urine which is full-coloured and abundantly rich in salts, and we must seek in some other direction for the cause of the morbid tendency. In these cases the chief determining factors are, I believe, to be found in the proportion of uric acid in the urine, and in the degree of acidity of the urine.

The influence of these two factors was investigated

[1] See a paper by Mr. C. Plowright, of King's Lynn, in the *Medical Times* for October 10, 1885. Mr. Plowright, on the evidence of some experiments by Mr. H. C. Brown, attributes the good effect of salt to its alleged property of increasing the solvent power of water on uric acid. This is, however, I am satisfied, on the ground of very exact determinations both by myself and others, not the correct explanation. The real action of salt is, I believe, as a retarder of the decomposition of the quadri-urates, as previously explained on page 45.

by a method which approximates pretty closely to the conditions of the actual clinical problem. In the earlier part of the lecture I showed that normal acid urines tended to deposit their uric acid sooner or later; and the inference was drawn that this inherent tendency was the same in kind (though less pronounced in degree) as the tendency existing in pathological gravel. If this inference be well founded, it follows that the controlling factors in the two cases are similar; and that the conditions which hasten or retard the precipitation of uric acid in a sample of urine preserved in a test-tube would, if they could be made applicable, hasten or retard the precipitation of uric acid in the urinary passages. The mode of experimentation was as follows:—A number of test-tubes were each charged with 10 cc. of a normal acid urine. One of them was a control tube, and had no addition made to it. To the others, additions were made of known quantities of various substances, of which it was desired to know the effects on the time of onset of uric acid precipitation. The contents of the tubes were protected against decomposing changes by the inclusion of a few drops of chloroform. The tubes were then corked and placed in the warm chamber at blood heat. The tubes were frequently examined, and the time when uric acid began to be deposited was noted. When the experiment was finished, the acceleration or postponement of precipitation in the several tubes, as compared with the control tube, was computed.

Proportion of uric acid in the urine.—A sharp distinction must be drawn between the proportion, or percentage, of uric acid in the urine and its rate of excretion—that is, the total quantity excreted per hour or per day.

The proportion of uric acid in the urine bears no

constant relation to the rate of its excretion by the kidneys. During the digestion and absorption of food the hourly discharge of uric acid reaches its highest level, but its percentage in the urine, although high, is not then at its highest, owing to the fuller volume of the urine at this time. On the other hand, after prolonged fasting and during sleep the hourly discharge of uric acid sinks to its lowest point, but its percentage in the urine touches its highest pitch. Again, the occurrence of uric acid gravel is not a reliable proof of an excessive output of uric acid; and it is certain that individuals may habitually discharge a daily amount of uric acid considerably beyond the average, and yet be quite free from the symptoms of gravel. Nor is such an occurrence even a sure indication that the urine contains an undue percentage of uric acid. Cases are sometimes encountered in which the urine is caught, as it were, in the very act of depositing uric acid gravel—cases in which the urine, as it is voided, sparkles with crystals of uric acid. On four occasions I have been able to estimate the uric acid in such urines. The results are shown in the following table:—

TABLE VIII.—*Showing the Percentage of Uric Acid in Four Urines which were in the Act of Depositing Uric Acid at the Moment of Emission.*

No. 1	contained	0·084	per cent.	of uric acid
No. 2	„	0·076	„	„
No. 3	„	0·032	„	„
No. 4	„	0·022	„	„

In the first and second cases the percentage of uric acid greatly exceeded the average; in the third case it was slightly below the average; and in the fourth case it was very much below the average.

Notwithstanding all this, it would be an error to sup-

pose that the quantum of uric acid excreted per day, and its proportion in the urine, are without influence on the formation of urinary concretions. It stands to reason that persons who daily void an excessive amount of uric acid must be more liable than those who only void the normal quantity to crises in which the percentage of that substance rises above the average; and it is susceptible of proof that, other conditions being favourable, a high percentage of uric acid in the urine becomes a potent factor in the determination of uric acid precipitation. The following observations may be taken as evidence on this point. A healthy urine, which had deposited a copious sediment of amorphous urates in a urine glass, was divided into two equal portions, A and B. A consisted of the lower portion, which contained the deposit; B consisted of the upper or supernatant portion. Both portions were warmed to blood-heat, and became thereby perfectly transparent. Both portions were identical save in one respect, namely, that A contained a much larger percentage of uric acid (in the form of quadri-urates) than B. The specimens were then tested by the method above described. Four test-tubes were charged, each with 10 cc. of urine, composed as follows:—

Test-tube No. 1 contained A alone; No. 2 contained equal volumes of A and B; No. 3 contained three volumes of A, and seven volumes of B; and No. 4 contained B alone. The four test-tubes were then corked and placed in the warm chamber at blood heat. The following table (IX.) exhibits the times at which uric acid began to precipitate in the several test-tubes.

Grade of acidity of the urine.—The degree of acidity of the urine exercises, as might have been expected, a powerful influence on the time of precipitation of uric acid. In some cases of gravel I found the acidity of the

TABLE IX.—*Showing the Influence of the percentage of Uric Acid on the Time of Onset of Uric Acid Precipitation.*

Contents of the test-tubes	Time when uric acid began to be precipitated
No. 1 contained A alone	2 hours
No. 2 „ equal vols. of A and B . .	4 „
No. 3 „ 3 vols. of A and 7 vols. of B .	8 „
No. 4 „ B alone	20 „

urine fully twice as high as the normal average; in two such cases the urine was found to decompose the purified amorphous urate as rapidly as distilled water; but when its acidity was reduced to the normal level by the addition of sodium carbonate, it had then no more power in this respect than healthy urine—showing clearly that in these cases the determining factor in the disorder was solely excess of acidity. It was also found, experimenting on normal acid urines, that the addition of an exceedingly minute quantity of an alkaline carbonate postponed the time of precipitation of uric acid very notably. The following table displays some of the results obtained by this mode of testing :—

TABLE X.—*Showing Postponement of Precipitation of Uric Acid by the addition of minute quantities of Alkaline Carbonates to the Urine.*

Additions made to the urine	Time when uric acid began to be precipitated	Postponement of precipitation
No. 1. Urine alone—control tube . .	2 hours	
No. 2. Urine + 0·04 per cent. Pot. Bicarb.	4 „	2 hours
No. 3. Urine + 0·04 „ Sod. Bicarb.	5 „	3 „
No. 4. Urine + 0·04 „ Lith. Carb. .	10 „	8 „

The quantities of the alkaline carbonates added in this experiment were so small that the reaction of the urine, as tested by litmus paper, was not sensibly affected, and yet the postponement of precipitation was very considerable—considerable enough, had the events occurred in the urinary passages, to make the difference between the occurrence and non-occurrence of gravel. It will be observed that the sodium carbonate acted more powerfully as a retarder than the potassium carbonate, and that the lithium salt acted more powerfully than either. This, however, was solely due to the difference in their atomic weights. When these salts were used in quantities proportionate to their saturating power, no difference could be detected between them. It need scarcely be said that when the carbonates were added in sufficient quantity to render the urine neutral or alkaline, no precipitation of uric acid took place.

The general results of the above inquiry into the factors which control the precipitation of uric acid in urine, and which operate to determine or to prevent the occurrence of pathological gravel, may be summed up in the two following propositions. The conditions of the urine which tend to accelerate the precipitation of uric acid are—high acidity, poverty in salines, low pigmentation, and high percentage of uric acid. And, conversely, the conditions which tend to postpone precipitation are —depressed acidity, richness in salines, richness in pigments, and low percentage of uric acid. On the interaction of these factors the occurrence or non-occurrence of uric acid gravel appears to depend; and the most important of these factors is the grade of acidity.

THERAPEUTICS OF URIC ACID GRAVEL

The treatment of calculous disorders at the hands of the physician must always in the main be of a preventive character. When concretions are once formed in the kidneys or bladder, and these are too large or too awkwardly lodged to be washed out by the flush of the urinary stream, there is little prospect that they can be dissolved away by imparting solvent qualities to the urine. In such circumstances we are constrained to have resort to surgical means; and it is a matter for congratulation that the brilliant advances in the surgery of the kidneys and bladder—advances largely due to the enterprise and skill of British surgeons—enable us now to face this alternative with greatly diminished anxiety. In the domain of prophylaxis, however, there remains to the physician a fruitful field of activity. Nowhere, perhaps, is the aphorism that 'prevention is better than cure' more pertinent than in the case of calculous concretions. The force—the chemical force—which is requisite to prevent the precipitation of uric acid in the urinary channels is almost infinitely small as compared with the force which is requisite to redissolve a concretion already formed.

In considering the medical treatment of uric acid gravel it is important to fix our eyes on the urine itself. There is, perhaps, too ready a disposition to look for the determining causes of gravel elsewhere than in the urinary function itself—in the stomach, or in the liver, or in some general constitutional vice. It should be borne in mind that uric acid gravel is constantly seen as an independent disorder, existing *per se* in persons who are in all other respects perfectly healthy. And if gravel

be, not unfrequently, complicated or associated with other morbid conditions, it only conforms in this respect to the common rule applicable to most other disorders.

There is, however, no doubt that there exists a special relation between uric acid gravel and gout; and the circumstance that uric acid figures as a common factor in both has led certain persons to the opinion that the two complaints are substantially one and the same. This notion is certainly not correct; and from a therapeutic point of view it is, I believe, a mischievous notion. It is a matter of common experience that many gouty people are never troubled with gravel; and conversely, that many subjects of gravel are never troubled with gout. In both complaints there is an aberration of uric acid; but the error is essentially different in the two cases, both in regard to its site and in regard to its nature. In gout the error occurs on *this* side of the kidneys, in the blood and tissues, and the uric acid is precipitated in a state of combination as a bi-urate; in gravel, the error occurs on *that* side of the kidneys, and the uric acid is precipitated in the urine and in the free state. In the former, the deposition takes place in the true interior of the economy; in the latter, the deposition takes place in what is, strictly speaking, the exterior of the economy, that is to say, on the surface of a doubling of the external integument. These differences are, I believe, radical, and involve important distinctions both in regard to pathology and in regard to treatment. The fact that gout and gravel sometimes exhibit a kind of vicarious correspondence, that the one complaint alternates with the other at different periods in the lifetime of the same individual, or in successive generations of the same family, while indicating an undoubted relation, indicates also at the same time an essential distinction.

Speaking from a somewhat long and large experience of these ailments, I cannot recall a single instance in which a paroxysm of gout and a paroxysm of uric acid gravel broke out synchronously. And Sir Alfred Garrod, with a longer and still larger experience, gives me his testimony to the same effect. Some pertinent evidence on the point we are debating has been brought forward by Mr. Plowright, of King's Lynn.[1] He remarks that, residing as he does in Norfolk, the chief stone district in England, he has been struck by the comparatively small number of cases of gout which have come under his notice as compared with the number of stone cases. He further shows, by reference to the Registrar-General's Reports, that there is no correspondence between the prevalence of gout and of stone in the several counties of England and Wales. Some of the counties which have a high death-rate from gout have a low death-rate from stone, and, conversely, counties with a high death-rate from stone; have a low death-rate from gout. In Scotland, where gout is rare, stone is comparatively common.

These considerations lead to the conclusion that gravel should be regarded as a primary vice of the urinary function; that it requires to be studied by and for itself; and that the urine is the proper and natural field for the investigation of its etiology and therapeutics.

We have just seen that the factors which chiefly control the precipitation of uric acid in the urine are—the degree of pigmentation, the proportion of salines, the percentage of uric acid, and, above all, the grade of acidity of the urine; and I shall consider the treatment

[1] *On the Cause and Distribution of Calculous Disease*, by Charles B. Plowright. London, 1886, p. 14.

solely with reference to the operation of these four factors.

With regard to the *deficiency of pigments* as a contributory factor in the promotion of uric acid gravel I have no facts or suggestions to offer which have a bearing on the therapeutical problem; and I doubt whether any help is to be got from further inquiry in this direction. The subjects of gravel among the well-fed population of this country, as far as my experience goes, present no deficiency of pigment in their urine.

With respect to the *proportion of saline matters* in the urine, it is worth bearing in mind that the facts gathered by Mr. Plowright, as well as the experimental evidence adduced by myself, point strongly to the suggestion that the subjects of gravel should be advised to take habitually with their meals as much culinary salt as their palates will tolerate. I may also remind those whose lot it is to practise among the children of the poor, or among the rice-eating populations of tropical and sub-tropical countries, that it would be well, in cases of gravel, to see that the patient's food should contain an adequate proportion of articles rich in saline materials, that is to say, of milk, meat, fish, eggs, and salads.

The *proportion of uric acid* in the urine, as a controlling factor in uric acid precipitation, demands somewhat more notice. It is a common notion that the occurrence of uric acid gravel depends simply on an excess of this substance in the urine (so-called uric acid diathesis). This assumption pervades the entire argument of most writers on gravel, and dominates all their plans of treatment. I have already shown that the assumption is only partially true, and that the percentage of uric acid is only a subordinate factor in the determina-

tion of uric acid precipitation. During the alkaline tide after meals the percentage of uric acid in the urine reaches a high level, and yet there is less risk of precipitation at this time than at any other period of the day. It has, moreover, been before demonstrated (*see* Table VIII. p. 51) that uric acid is sometimes thrown down in the urinary channels when its proportion in the urine does not exceed the normal average, or even when it falls considerably below that average. At the same time it is true, that when other favouring conditions coincide, a high level of uric acid excretion with a high percentage of it in the urine is a valid factor in the production of gravel, and that a lowering of that level, if by any means attainable, is an important therapeutical indication. Attempts have been made in this direction by modifications of the diet and regimen. The advice given on this head by various writers is, however, very contradictory. Some recommend that the subjects of uric acid gravel should avoid sugar and fruit and fat; others that they should take fat in abundance and avoid starchy matters; some advise a vegetarian diet, others a mixed diet. The most reliable investigations indicate that fat, sugar, and starchy matters have not the slightest direct influence on the production and excretion of uric acid, nor has any proof been given that albuminoid substances of vegetable origin differ in this respect from albuminoid substances of animal origin. The only point that has really been made out is this: that the excretion of uric acid is diminished by lessening the albuminoid ingredients of the food, and that it is heightened by increasing these ingredients. But this class of aliments are absolutely essential to nutrition, and you cannot diminish them to any serious extent without injuriously affecting the

nutritive equilibrium. After a careful examination of all the evidence on this point, it appeared to me that the practical outcome was only this: that persons who are subject to uric acid gravel, and who are also troubled with a large appetite, should seek to allay their cravings and to lessen the intake of nitrogenous material by the free use of farinaceous articles of food, with salads, fruit, and garden vegetables, all of which are comparatively poor in albuminoid constituents. I shall again revert to this subject in my fourth lecture, when speaking of the dietetic treatment of gout.

I am satisfied, from repeated observations, that in the immense majority of cases of uric acid gravel in this country, the immediate determining cause of the precipitation is *excessive acidity of the urine*, and that the paramount indication of preventive treatment is to diminish this acidity. All other schemes of treatment sink into insignificance in comparison with this. The use of alkalising agents for the prevention of uric acid gravel stands on a perfectly rational basis. It is chemically impossible for uric acid to be deposited from an alkaline urine; it may even be said that it is impossible for uric acid to be deposited prematurely, that is to say, within the urinary channels, from a neutral or feebly acid urine. And as we possess the means of harmlessly reducing the acidity of the urine at pleasure, we have in our hands, in principle at least, the absolute power of preventing uric acid gravel. There are, however, some practical difficulties to be overcome. The disposition to uric acid gravel has a certain persistency. It may last intermittently for months or years; and it would obviously be too great a strain on a treatment which is purely protective to require that a patient should take antacid medicines in

sufficient doses and at sufficiently short intervals to maintain the urine continuously alkaline or neutral over so long a period of time. Nor is any such effort necessary. A study of the normal oscillations of the urine at different periods of the day and night leads to the inference that the liability to uric acid gravel rises to a dangerous intensity only during certain limited portions of the twenty-four hours. The risk in gravel is almost confined to precipitations which take place within the precincts of the kidneys. Precipitations which take place in the bladder are harmlessly swept out at the next act of micturition. These latter probably only do harm when there is already a stone in the bladder to which the crystals can accrete, or when a pouch exists in the viscus to receive and detain the deposit. What most concerns us, therefore, is the state of the urine as secreted by the kidneys, rather than the state of the product accumulated in the bladder. For the sake of brevity, and by way of distinction, we may be allowed to speak of *renal urine* and *vesical urine*. These two products, no doubt, usually correspond sufficiently closely to enable us to judge from the urine of micturition what the character is of the urine secreted by the kidneys, but this is not always the case. Vesical urine represents the aggregate work of the kidneys for several consecutive hours. During this interval the renal urine may have undergone sharp oscillations—from acid to alkaline, from dilute to concentrated, from richness to poverty in uric acid—but the vesical accumulation, which is at length discharged by micturition, will have a mean or average composition which entirely masks these oscillations. To arrive at a correct knowledge of the state of the urine as it flows from the kidneys, it is necessary to obtain the secretion and to examine it at short intervals. Some

years ago I made an extended series of observations on these lines. The subject of experiment was a healthy man of twenty-eight. The urine was collected at hourly, or at most two-hourly, intervals throughout the twenty-four hours—except during the period of sleep, which was taken as a single interval. The inquiry embraced observations on thirty-two complete days, besides a good many more on portions of days. The results of the investigation were incorporated in two papers published in the 'Memoirs of the Manchester Literary and Philosophical Society'[1] and in the 'Edinburgh Medical Journal.'[2] Some of the conclusions arrived at have a direct bearing on the preventive treatment of urinary gravel. The character of the urine was shown to be most affected by the digestion of food, by prolonged fasting, and by sleep. It was found that a meal, whether it was composed of ordinary mixed food, or of purely animal or purely vegetable substances, produced two constant effects. It depressed the acidity of the urine and increased its volume. And, conversely, prolonged fasting raised the acidity and diminished the flow of the urine. During the hours of sleep, which are also, of course, hours of fasting, the acidity of the urine reached its highest point, and the flow of the urine reached its lowest point. The proportion of uric acid in the urine, that is to say, its percentage, was found highest during the time of sleep; but the hourly excretion was highest during the hours following a meal. Now, if we apply these facts in the light of the evidence previously adduced in regard to the factors which determine the

[1] 'A Contribution to Urology,' *Memoirs of the Literary and Philosophical Society of Manchester*, vol. xv.

[2] 'On Some of the Daily Changes of the Urine,' *Edinburgh Medical Journal*, 1860.

precipitation of uric acid in the urine, we arrive at the conclusion that the period when there is most risk of precipitation in the kidneys is during the time of sleep, and especially in the early morning, during the two or three hours preceding breakfast. The deposition of uric acid is most imminent when there is a conjunction of the several favouring conditions—that is to say, when the flow of urine is very scanty, when the secretion is hyperacid, and when it is rich in urates. Such a conjunction is most fully developed during the period of sleep. Sleep is a time of fasting, and, therefore, a time of hyperacidity of the urine—a time of recumbency and bodily immobility, and, therefore, a time when the renal stream approaches nearest to stagnation, and loiters longest about the purlieus of the kidneys. On the other hand, during the day and the waking hours the recurrence of the meals keeps the urine at a low degree of acidity, or even renders it for a time neutral or alkaline; the renal stream is comparatively full and rapid, and its descent from the kidneys is favoured by the force of gravity. During these hours, therefore, the risk of uric acid precipitation is reduced to a minimum, even in persons who have a distinct tendency that way. For, as I have repeatedly had occasion to observe, the urine of calculous subjects exhibits precisely the same cyclical diurnal variations as that of healthy persons, though not always in so marked a degree.

A study of these facts indicates that if we safeguard the night, the day may be generally left to take care of itself. This theoretical deduction is fully in accordance with experience in the treatment of uric acid gravel. In the milder cases a single full dose of the alkalising agent taken at bedtime suffices to prevent the recurrence of the colicky pains and the discharge of uric acid concre-

tions. For this purpose the citrates and bicarbonates of potash and soda are the most effective. The citrate of potash is, on the whole, the best preparation to employ; it has very little taste, and it sits comfortably on the stomach. The dose for an adult should not be less than 40 to 60 grains dissolved in three or four ounces of water. In severer cases a single dose is insufficient, and the early morning urine will still exhibit a morbid disposition to precipitate uric acid. In such cases a second dose should be taken about the middle period of the hours of sleep. This is less difficult to manage with the subjects of gravel than in healthy persons. There is commonly in calculous subjects a certain restlessness and a certain irritability of the urinary organs, which leads to an increased frequency of micturition, and such persons rarely pass the night without a call to empty the bladder. Advantage should therefore be taken of this break in the continuity of sleep to take the second antacid dose. In this way the entire night and early morning may be effectually guarded.

Cases of uric acid gravel, however, are not always to be got rid of on these easy terms. Now and then instances are met with in which the perversion is so great that the urine is disposed to deposit almost the day through, and in which the normal alkaline tide after meals seems to be well-nigh abrogated. Under these circumstances, additional doses of the antacid are required to afford the requisite protection; and the right times for these doses are some two or three hours after breakfast, and some two or three hours before the last meal of the day. But, so far as I have seen, these extreme conditions only last a short time—a few days at most—and there is then a return to a less urgent state of things.

It is, indeed, a marked character of uric acid gravel that it oscillates in intensity—it comes and goes in paroxysms, reminding one of the waviness of gouty phenomena. For this reason it is desirable to frequently note the state of the urine, and to ascertain its greater or less proneness to deposit uric acid, so that the administration of the antacid may be adjusted to the actual needs of the patient. There is no great difficulty about this. If a freshly-voided specimen of the urine of fasting—say the urine of the early morning or the urine secreted just before dinner—be set aside in a test-tube, in a warm place (so as to prevent the deposition of the amorphous urates), the imminence of precipitation can be easily observed. If precipitation be morbidly imminent, crystals of uric acid will appear perhaps at once, perhaps in an hour, or a couple of hours. If precipitation be not morbidly imminent, crystals will not appear for several hours, perhaps not for two or three days. It is possible in this way to gauge pretty accurately the intensity of the morbid tendency, and to regulate thereby the amount and frequency of the antacid doses, or to decide on their discontinuance.

There are still some points in regard to the use of alkalies in gravel on which additional information is needed. We want to know more precisely the length of time over which a dose of alkali extends its influence on the urine, the amount of dose required to reach an effective result, and the relative alkalising potency of the different preparations in use. Dr. Luff has, at my suggestion, undertaken an inquiry with a view of clearing up these points. His investigation is not yet complete, but he has already arrived at some results of interest, which he permits me to mention. He finds that a dose of 40 grains of citrate of potash taken at 11 P.M. extends its influence through the night and up to eight

o'clock next morning. The effect on the morning urine was, however, very slight. A dose of 60 grains had a more considerable effect, and often rendered the morning urine actually alkaline. Bicarbonate of potash acted in an exactly equivalent degree with the citrate. A corresponding dose of the acetate of potash appeared to act more rapidly, and its effect was less enduring than that of the citrate. The carbonates of lime and magnesia were found to be quite ineffective as alkalising agents on the urine.

A point of some importance in the management of cases of uric acid gravel is the *arrangement of meal-times*. Each meal acts on the urine as a dose of alkali, and also as a diluent, and in both these ways operates as a protection against uric acid precipitation. After the meal is absorbed and assimilated, the urine becomes again increasingly acid and concentrated, and, as a consequence, increasingly prone to precipitate uric acid; subjects of gravel should, therefore, be warned not to allow too long an interval to elapse between their meals. This precaution is especially needed as regards the interval between breakfast and the midday meal. The first meal of the day is, with most persons, very quickly digested, and its effects on the urine are correspondingly transient. At no time during the waking hours does the acidity of the urine tend to rise so high, and its volume to fall so low, as in the later portion of the interval between the first and second meal of the day. This interval should, therefore, be abridged. In this connection the pleasant institution of afternoon tea may come in for a word of commendation, as serving to break the sometimes too long interval between luncheon and a late dinner. Some people interpose an unconscionable interval, of twelve or fourteen hours, between their last meal at night

and their breakfast next morning. This is a very risky practice in the case of calculous subjects.

The essential thing in the prophylactic treatment of uric acid gravel is to guard the urine from precipitating within the precincts of the kidney. And we shall practically have attained our object if we succeed, not in altogether preventing precipitation, but in postponing it until the urine has quitted the kidneys. A postponement for a short time, even half an hour, may make all the difference between a precipitation which is fraught with pain and peril, and a precipitation which is practically harmless. Now, the protective effect of an antacid extends in this respect a good deal beyond the point at which the urine is rendered actually alkaline. For although all acid urines of medium density precipitate uric acid sooner or later, the time of the occurrence of that precipitation is immensely influenced by the degree of acidity of the urine. Other things being equal, the more acid the urine, the earlier is the precipitation ; and the less acid the urine, the longer is the precipitation postponed. An antacid effect, therefore, which is too feeble to render the urine actually alkaline may be quite sufficient to depress its acidity to such a degree as shall postpone the time of precipitation until the urine has escaped from the kidneys, and even from the bladder.

Effect of water and mineral waters on uric acid precipitation.—It might appear at the first blush that the easiest and simplest way of combating the tendency to uric acid gravel was by the free drinking of watery fluids. The kidneys—the healthy kidneys—have an almost unlimited power of separating water from the blood. When water is freely taken into the stomach, it is rapidly absorbed, and passes speedily, as through a sieve, by the kidneys into the urine, and so dilutes it. By thus en-

larging the volume of the urine, its degree of acidity and its percentage of uric acid are proportionately reduced, and its tendency to precipitation thereby lessened. But, on the other hand, by diluting the urine, its degree of pigmentation and its proportion of saline ingredients are diminished, and both these effects tend to promote the precipitation of uric acid. Diluting the urine is thus seen to be a two-edged weapon, and may in certain contingencies do more harm than good. Of course, if the dilution be carried very far, to the extent of lowering the concentration to one-third or one-fourth of the normal degree, the preventive effect preponderates, and the percentage of uric acid is so reduced that precipitation of it becomes impossible. The record of an actual experiment will serve to bring out these points. A sample of urine from a man disposed to uric acid gravel was divided into three portions, A, B, and C. A had no addition made to it, B was diluted with an equal bulk of water, and C was diluted with four times its bulk of water. The specimens were then set aside in test-tubes in the warm chamber. A threw down uric acid in six hours, B in three hours, and C not at all. Contingencies of this sort must, however, be uncommon. In the great majority of cases the effect of dilution, even of moderate dilution, would, no doubt, be to lessen the risk of precipitation.

There is, however, another point in regard to the use of water as a preventive of gravel which is more important. The effect of water-drinking on the flow of the urine is of extremely brief duration. Water is absorbed from the empty stomach and passes out through the kidneys so quickly, that in a couple of hours, after even very free potation, the surplus water is entirely removed and the urine is again restored to its original concentra-

tion, and the liability to precipitation returns. If the imbibition of water could be continued at short intervals, and maintained over the twenty-four hours, this would doubtless be an effective means of guarding against uric acid gravel; but this would be an onerous proceeding, and would even be impossible during the hours of sleep. I think, therefore, on both these grounds that water-drinking has only a limited application in the prophylactic treatment of gravel.

The use of *mineral waters* is open to the same criticism as that of ordinary water. Their effect is transitory, and cannot be regarded as in any degree curative of the disposition to gravel. A distinction must, however, be drawn between the alkaline springs and the non-alkaline springs. Alkaline waters, such as those of Vichy, which are largely impregnated with carbonate of soda, have the power of alkalising the urine, and therefore absolutely protect against uric acid gravel during the period of their use. But the non-alkaline waters have no such power, and their beneficial action is due to the fact that they greatly increase the flush of the urinary stream, and thereby promote the carrying down of concretions already lodged in the precincts of the kidneys. Their efficacy in this direction is quite undoubted; but it is, I think, equally undoubted that the drinking of equivalent quantities of distilled water would be just as efficacious. A glance at the composition of the several non-alkaline springs which have acquired renown in the treatment of gravel supports this view; and indicates that the neutral salts contained in them have little to do with their efficacy. Some of these waters are impregnated with sulphate or chloride of sodium, others with salts of magnesia; others, again, only contain minute quantities of sulphate of lime, and are scarcely

distinguishable, except for their warm temperature, from ordinary drinking-water. Yet all these most diverse springs claim equal powers in cases of gravel. Is it not plain that what chiefly gives them efficacy is that which they all contain in common, namely, their watery constituent? Subjects of urinary gravel who pay, as many of them do, an annual visit to one or other of these springs imagine that such a visit clears them from their calculous tendency for the rest of the year. This, I believe, is a delusion. Such persons, on their return home, stand, in regard to their morbid proclivity, precisely where they stood before their visit.

It is obvious that a preventive treatment of uric acid gravel, to be completely effective, should be available all the year round, and be capable of timely application whenever the emergency arises. An adequate choice of substances which alkalise the urine is always at our disposal; their power of preventing uric acid precipitation amounts to a chemical certainty; and in even moderately prudent hands no harm can follow from their use. I see no reason, provided vigilant watch be kept on the imminence of uric acid precipitation in the fasting urine, in the manner before described, why sufferers from this kind of gravel should not, by a prompt resort to antacid remedies, be able at all times to protect themselves effectually against fresh formation of uric acid concretions—and thereby save themselves from a world of pain and danger.

LECTURE III

CHEMISTRY OF URATIC PRECIPITATION IN GOUT

Mr. President and Gentlemen,—The chemistry of gout in its full extension embraces changes of the most diverse character in the blood and tissues. I do not propose to deal with the subject in this comprehensive sense, but to confine myself entirely to the relations of gout with uric acid. By far the most characteristic feature of gout is the formation of chalk-like deposits in certain parts and tissues of the body, especially in and about the joints. The essential component of these deposits is bi-urate of sodium, and it is always present in the crystalline condition. The crystals are distributed through the implicated tissue in the form of delicate needles, aggregated into tufts, bundles, and stars. The arthritic incidents of gout may be said, not improperly, to be simply incidents pertaining to the precipitation of these crystals in the structures of the joints. Without the occurrence of this precipitation the gouty paroxysm could not take place, nor could the more chronic changes in the joints, with their train of attendant symptoms, follow after. Were it possible for us to keep the sodium bi-urate in a state of solution in the bodily fluids, the clinical portraiture of gout would be completely transfigured. Whatever other manifestations of the gouty constitution we might have to deal with, we should not have to contend with this most grievous outcome of the

diathesis. The evidence brought forward by Sir Alfred Garrod on this point appears to me to be conclusive, and justifies the deduction that the deposition of the crystalline bi-urates is not merely a concomitant, but is the actual cause of the joint-troubles of gout. This view is now pretty generally accepted, and forms the basis of most of our plans of treatment in the management of the gouty state.

Hence it is that the history and chemical properties of sodium bi-urate have acquired a capital importance in the pathology of gout. We are interested to know how this compound arises in the body from nascent uric acid; what are its relations of solubility in diverse media, and more particularly in the blood and lymph and synovia; and what are the factors which tend to determine its precipitation in the body, or tend to prevent its precipitation. The elucidation of these questions involves a complicated inquiry; and what I have to offer is not a complete exposition of these difficult problems, but rather a contribution thereto, and, more especially, a contribution towards the methods to be followed in seeking their elucidation.

I have before adduced evidence to show that the normal or physiological condition of uric acid in the body is that of a quadri-urate, and that any departure from this condition must be regarded as pathological. In the last lecture I traced the changes which the quadri-urate undergoes in the urine, and which lead up to the separation of uric acid in the free state as gravel and urinary sediments. In the present lecture I shall endeavour to trace the converse changes which the quadri-urate undergoes in the blood and lymph, and which lead up to the formation and deposition of sodium bi-urate in the tissues.

In order to effect this purpose I propose, first, to examine the solubility of the material of gouty concretions, namely sodium bi-urate, in various media—in the serum of the blood, in synovia, and in diverse saline solutions—then to examine and compare the behaviour of free or uncombined uric acid with the same media. Upon the basis of the results thus obtained I shall be able to formulate a general theory of uratic precipitation.

SOLUBILITY OF SODIUM BI-URATE [1] IN DIVERSE MEDIA—(*a*) IN WATER, (*b*) IN BLOOD-SERUM AND KINDRED MEDIA, (*c*) IN VARIOUS SALINE SOLUTIONS

(*a*) *Solubility of sodium bi-urate in water.*—When sodium bi-urate is digested at blood heat with pure water it enters pretty freely into solution. Such a solution, if fully saturated, throws down a copious precipitate of uric acid when treated with acetic or hydrochloric acid. Careful experiments indicated that the solubility of sodium bi-urate in distilled water, at 100° F., approximated very closely to the proportion of 1 part in 1,000. This was taken as the standard of comparison in estimating the solubility of this compound in all other media.

(*b*) *Solubility of sodium bi-urate in blood-serum.*—Sodium bi-urate is very sparingly soluble in the serum of the blood, as is shown by the following experiments. Sodium bi-urate in excess was treated with blood-serum

[1] Sodium bi-urate was prepared by boiling four grams of uric acid in 400 cubic centimetres of a 1 per cent. solution of sodium bicarbonate. This was filtered hot and then allowed to stand for twenty-four hours. A copious precipitate of crystalline stars and needles was thus obtained. This was thrown on a filter and washed with cold distilled water, and then dried at 100° F. In experimenting with the urates the investigator should always prepare his own materials. Samples of the urates supplied to me by dealers proved to be mere crude mixtures of uric acid with the bases, and were wholly unfit for exact experiments.

of the horse and pig in corked phials. The phials were placed in the warm chamber and frequently agitated. After a digestion of twelve hours the supernatant serum was filtered twice through a threefold filter.[1] The filtrate thus obtained, when acidulated with acetic acid, gave not the slightest precipitation of uric acid. Nevertheless, some slight solution had taken place. For when a portion of the filtrate was evaporated on a watch-glass in the warm chamber to near dryness, needles of bi-urate could be readily detected in it under the microscope; or, when the filtrate was tested with Garrod's thread experiment, crystals of uric acid were always found sprinkled on the thread. It thus appears that sodium bi-urate, although very sparingly soluble, is not absolutely insoluble, in blood-serum. From a number of comparative experiments, I estimated that at blood heat the amount dissolved was probably about 1 part in 10,000.

Results of a corresponding character were obtained with actual uratic deposits. A metatarsal bone, encrusted on its articulating surfaces with chalky matter, from the body of a gouty man was suspended in a phial containing six ounces of blood-serum of the pig. A few drops of chloroform were added to prevent decomposition, and the phial tightly corked. This was placed in the warm chamber for a fortnight, and afterwards kept on a shelf in my sitting-room. The serum was renewed three times. No appreciable change in the deposit was observed for a very long time. Even after the lapse of eight months the encrusted matter did not appear diminished. Nevertheless, slow solution was taking place. At the end of twelve months there was a visible diminution, and in fifteen months the deposit was entirely

[1] The needles of sodium bi-urate are so minute and delicate that some of them pass through the filter unless the most stringent precautions are taken.

dissolved out. In strong contrast with this was the behaviour of water. A second metatarsal bone from the same subject, and similarly encrusted, was suspended in six ounces of distilled water and treated in the same way. The deposit was entirely dissolved out in four days.

The behaviour of sodium bi-urate with synovia corresponded exactly with its behaviour with blood-serum —only minute traces went into solution.

It was ascertained by direct experiment that the behaviour of uric acid and its compounds with blood-serum depended entirely on the saline ingredients contained in it, and had no relation to its albuminous constituents. When the serum was deprived of its salts by dialysis, it was found that it reacted with uric acid and the urates like simple water; and the same rule holds good, no doubt, with regard to all the bodily fluids. An examination of the saline components of these fluids is, therefore, of prime importance in the study of the chemistry of gout.

The serum of the blood, and its derivatives, lymph and synovia, although differing considerably from each other in their albuminous elements, are almost identical in regard to both the quantity and the quality of their saline constituents. These latter are remarkable for the immense preponderance of sodium salts. The subjoined table exhibits the average proportion of the several saline ingredients contained in blood-serum :—

TABLE XI.—*Showing the Percentage of the several Salts in Blood-Serum.*

Sodium Chloride	0·50 per cent.	Sodium Salts = 0·73 per cent.	
Sodium Bicarbonate	0·20 ,,		
Sodium Phosphate	0·03 ,,		
Potassium Salts	0·06 ,,	All other Salts = 0·11 per cent.	
Calcium Salts, Magnesium Salts	0·05 ,,		

The fact just mentioned—namely, that the reactions of the bodily fluids with uric acid and the urates depend exclusively on the saline ingredients contained in them, suggested the idea that advantage might be taken of this circumstance to facilitate the chemical study of gouty precipitation. If a solution in water of the salines of blood-serum were prepared, such a solution might be expected to behave with uric acid and the urates like the serum itself—and this proved on trial to be the case. An examination of the above table shows that the salts of sodium exceed the aggregate of all the other salts of blood-serum, in the proportion of seven to one. And practically, for the purpose in view, the saline basis of blood-serum might be considered as consisting essentially of sodium chloride and sodium carbonate, so greatly do these preponderate over the sum of all the other salts put together. From these particulars it may be deduced that a solution in water containing chloride and bicarbonate of sodium,[1] in the proportion specified in the table, would be a fairly exact representation of blood-serum, in so far as its saline ingredients are concerned. And it was found experimentally that such a solution reacted with uric acid and the urates in the same manner as blood-serum itself, and in the same manner as a solution comprising all the salines of the serum in their due proportions as ascertained by the best analyses. Accordingly, a solution was prepared in conformity with these indications, and was designated as the *standard solvent*, or *standard solution*. Its composition was as follows :—

[1] The small proportion of sodium phosphate was neglected, both for the sake of simplicity and because it was experimentally ascertained that its presence or absence did not in the least affect the solvent properties of the solution on uric acid and the urates.

TABLE XII.—*Showing the Composition of the Standard Solvent.*

Sodium Chloride	0·5 gram
Sodium Bicarbonate	0·2 „
Distilled water	100 cubic centimetres

This solution was much used in the present research, especially as a pioneer. For experimental purposes it possessed certain advantages over serum and synovia. Its composition could be more easily modified by additions to it, or subtractions from it; the quantities of uric acid and urates taken up by it could be more exactly estimated, and its limpidity permitted the first signs of precipitation to be more readily detected. The behaviour of uric acid and the urates with this solvent was studied in detail, under varying conditions of temperature and time, and with varying modifications of its composition. The results thus obtained were afterwards collated with those obtained with blood-serum in similar circumstances, and with parallel modifications of its composition.

The standard solvent was found to behave with sodium bi-urate in exactly the same way as blood-serum. Only the minutest traces of the bi-urate were taken up by it at 100° F. Such a solution, when carefully filtered, gave no precipitate of uric acid when treated with hydrochloric acid.

(*c*) *Solubility of sodium bi-urate in saline solutions.*—The influence of different saline substances on the solubility of sodium bi-urate has not only a pathological, but also a therapeutical bearing. Saline substances are largely used in the treatment of gout, both in the guise of pharmaceutical preparations and as constituents of mineral springs, under the belief that they promote the

holding in solution of the peccant bi-urate, and thereby hinder its deposition as gouty concretions, and even favour the re-solution of concretions already formed. It is, therefore, of practical interest for us to know what kinds of salts, if any, act favourably, and what kinds act unfavourably, in this respect. A large series of experiments were undertaken with a view of elucidating this point, and the deductions indicated are, I venture to think, of considerable interest. The salts of which the effects were investigated were those of sodium, potassium, calcium, magnesium, and ammonium. In regulating the dosage of the salts in the solutions examined, regard was had to the possibilities of the pathological and therapeutical problems involved. The experiments were carried out in the following manner. Solutions of known strength of the salts to be tested were prepared in distilled water. These solutions were digested at blood heat with excess of sodium bi-urate in corked flasks. The flasks were then placed in the warm chamber, and maintained at 100° F., with frequent agitation, for five hours. The supernatant liquid was then carefully filtered off. In some cases repeated filtration through a threefold filter was required in order to obtain a perfectly transparent product. Finally, the percentage of uric acid in the filtrate was estimated, and calculated as sodium bi-urate. The results thus obtained are exhibited in the following tables. The solubility of the bi-urate in distilled water is placed at the head of each table as a standard of comparison.

Salts of sodium.—The effects of the following soda salts were investigated—namely, the bicarbonate, chloride, sulphate, phosphate, and salicylate. All these salts showed a powerful influence in diminishing the solvent power of the medium on the sodic bi-urate; and the

adverse influence increased progressively, up to a certain point, with the increasing strength of the solution.

TABLE XIII.—*Showing the Influence of Sodium Salts on the Solubility of Sodium Bi-urate at* 100° *F.*

Solvent	Sodium bi-urate dissolved[1]
Water	1·00 per 1,000
Water containing :—	
0·1 per cent. Sod. Bicarb. . . .	0·50 „
0·2 „ „ . . .	0·34 „
0·3 „ „ . . .	0·20 „
0·5 „ „ . . .	0·13 „
0·7 „ „ . . .	0·09 „
1·0 „ „ . . .	0·08 „
0·1 „ Sod. Chloride . . .	0·45 „
0·2 „ „ . . .	0·30 „
0·3 „ „ . . .	0·16 „
0·5 „ „ . . .	0·10 „
0·7 „ „ . . .	0·08 „
1·0 „ „ . . .	0·05 „
0·1 „ Sod. Sulph. (cryst.) . .	0·55 „
0·5 „ „ „ . . .	0·24 „
0·1 „ Sod. Salicylate . . .	0·65 „
0·3 „ „ . . .	0·36 „
0·5 „ „ . . .	0·25 „
0·1 „ Sod. Phosph. (cryst.) .	0·70 „
0·5 „ „ „ . .	0·32 „

The table indicates that the degree of alkalescence of the medium, or its neutrality, had not the slightest influence on the result. The carbonate and phosphate, which have an alkaline reaction, acted exactly in the same way as the chloride and sulphate, which have a neutral reaction.

It may be observed that the sodium chloride had a more marked effect than the other sodium salts—more

[1] The estimations of uric acid in this and the following tables were mostly made by the usual gravimetric process with hydrochloric acid. When the quantity dissolved was too small for weighing, it was estimated by a minimetric adaptation of the method of Arthaud and Butte.

than the bicarbonate, but especially more than the sulphate, phosphate, and salicylate. This difference is, however, solely due to the larger percentage of the metal in the chloride. When solutions were prepared of these several salts in such proportion that the percentage of sodium in them was constant, their effect was found to be as nearly as possible equivalent.

It may also be noticed, comparing solutions of the bicarbonate and chloride, that the deterrent effect approached its maximum with solutions containing 0·5 per cent. Above this strength the deterrent effect increased but slightly.

Salts of potassium.—Solutions of the following potassium salts were subjected to examination—namely, bicarbonate, chloride, and phosphate. The results stand in the strongest contrast with those obtained with sodium salts.

TABLE XIV.—*Showing the Influence of Potassium Salts on the Solubility of Sodium Bi-urate at* 100° *F.*

Solvent	Sodium bi-urate dissolved
Water	1·00 per 1,000
Water containing:—	
0·1 per cent. Potass. Bicarbonate . .	0·96 „
0·2 „ „ „ . .	1·00 „
0·3 „ „ „ . .	1·00 „
0·5 „ „ „ . .	0·97 „
0·7 „ „ „ . .	1·02 „
1·0 „ „ „ . .	0·98 „
0·1 „ Potass. Chloride . .	0·96 „
0·3 „ „ „ . .	1·01 „
0·5 „ „ „ . .	1·10 „
0·1 „ Potass. Phosphate . .	1·01 „
0·5 „ „ „ . .	1·00 „

The experiments tabulated indicate that the salts of potassium exercise no influence, neither for nor against,

on the solubility of the bi-urate. The results came out, within the necessary limits of error, precisely as with distilled water. The bicarbonate and phosphate, which have an alkaline reaction, behaved exactly in the same way as the chloride, which has a neutral reaction. The varying strengths of the solutions made not the least difference.

The difference between solutions of sodium salts on the one hand, and those of potassium salts or distilled water on the other, is so conspicuous that it is easily perceived without any resort to quantitative analysis. A 0·7 per cent. solution of any of the sodium salts (reckoned as anhydrous) dissolves so little of the bi-urate that saturated solutions made at blood heat show no precipitation of uric acid when treated with hydrochloric acid, or at most only a few scattered crystals at the end of forty-eight hours; whereas similar solutions made with potassium salts, or with distilled water, become almost at once milky when treated with hydrochloric acid, and, in a few minutes, throw down an abundant deposit of uric acid.

Calcium, magnesium, and ammonium salts.—The addition of calcium, magnesium, and ammonium salts diminished the solvent power of water on sodium bi-urate. The subjoined table exhibits the results obtained with these three classes of salts.

The table shows that calcium salts exercise a strongly deterrent effect on the solvent power of water on sodium bi-urate, approaching in this respect but not equalling the sodium salts. The magnesium salts, on the other hand, although exhibiting a distinctly deterrent influence, approach more nearly to the indifferent reaction of the potassium salts. The salts of ammonium were found

to stand in an intermediate position between those of calcium and magnesium.

TABLE XV.—*Showing the Influence of Calcium, Magnesium, and Ammonium Salts on the Solubility of Sodium Bi-urate at* 100° *F.*

Solvent	Sodium bi-urate dissolved
Water	1·00 per 1,000
Water containing:—	
0·1 per cent. Calcium Sulph. . . .	0·65 ,,
0·2 ,, ,, ,, . . .	0·44 ,,
0·5 ,, Calcium Chloride . .	0·27 ,,
0·1 ,, Magnesium Sulph. (cryst.)	0·90 ,,
0·1 ,, Magnesium Chloride . .	0·85 ,,
0·5 ,, ,, ,, . . .	0·68 ,,
0·1 ,, Ammon. Chloride . .	0·85 ,,
0·2 ,, ,, ,, . . .	0·50 ,,
0·3 ,, ,, ,, . . .	0·42 ,,
0·5 ,, ,, ,, . . .	0·35 ,,

Reviewing these results as a whole, the following conclusions may be deduced, in regard to the solubility of sodium bi-urate in simple saline solutions, at the temperature of the body :—

a. The influence of a salt depends exclusively on the nature of the base, and has no reference to the acidulous radicle with which the base is combined.

b. Salts with an alkaline reaction, such as carbonates and phosphates, do not differ in the least from neutral-reacting salts, such as chlorides and sulphates.

c. The salts of sodium exercise a strong deterrent influence, and the deterrent influence increases with the increasing percentage of the salts in solution. Salts of calcium, magnesium, and ammonium have also a deterrent effect, but

slighter than that of salts of sodium. Salts of potassium have no effect either way.

BEHAVIOUR OF URIC ACID WITH BLOOD-SERUM AND THE STANDARD SOLVENT, AND WITH SYNOVIA

An examination of the behaviour of free or uncombined uric acid with blood-serum and kindred media is a necessary part of the study of the chemistry of gout. It is only by knowledge thus gained that we can hope to elucidate the mode in which sodium bi-urate originates in the body, and learn something of the conditions which control its precipitation in the gouty system.

The reactions of free uric acid with blood-serum and synovia, and with the standard solvent and its modifications, are of quite a different kind from those of sodium bi-urate with the same media. In the latter case there is simply an act of solution. The bi-urate is taken up substantially unchanged, and the questions we had to decide were as to its degrees of solubility in the several menstrua. But when free uric acid is brought into contact with blood-serum and kindred media, there occurs not merely an act of solution, but a series of chemical reactions. Uric acid first enters into combination with the bases contained in the media; these new combinations then pass into solution, and subsequently undergo ulterior changes which it is of much interest to follow.

Behaviour of uric acid with blood-serum and the standard solvent.—When uric acid is digested, at the temperature of the body, with blood-serum or with the standard solvent, it passes freely into solution in combination with a base. In the course of an hour, with due agitation, the media will, on analysis, be found to have

taken up uric acid in the large proportion of about 1 part in 500. The chemical and solvent power of these media on uric acid depends on the sodium carbonate contained in them, and not on the sodium chloride; for a solution of the latter salt alone has no more action on uric acid than pure water. On the other hand, a solution containing sodium bicarbonate alone has precisely the same action on uric acid as when it is associated, as in the serum and standard solvent, with sodium chloride. The question now arose: What is the combination in which uric acid enters into solution? It could not be bi-urate, because crystalline sodium bi-urate is almost insoluble in these media; nor could it be neutral urate, because the neutral urates cannot arise in the presence of carbonates. The presumption remained that the combination is a quadri-urate. It was, however, highly desirable to have direct proof of this, and this was found to be difficult, owing to the instability of the quadri-urates. When freshly-made solutions of uric acid in the standard solvent were evaporated to dryness—no matter at what temperature—the recovered urate was always found in the condition of bi-urate. The reason of this was, that as evaporation proceeded, the solution became necessarily more and more rich in regard to its content of sodium carbonate, and thereby, as was afterwards found, more and more active in changing quadri-urate into bi-urate. I failed altogether, by various attempts at precipitation—by cautious addition of acids of diverse kinds, adding absolute alcohol, ether, glycerine, &c.—in throwing down a quadri-urate. I succeeded at length, by taking advantage of the great difference of solubility of quadri-urates at different temperatures, in obtaining direct evidence that uric acid was taken up by solutions of the alkaline carbonates in the state of quadri-urate.

The following experiment appears to be conclusive on this point. Uric acid in excess was digested at blood heat with a 1 per cent. solution of sodium bicarbonate, under constant agitation, for twenty minutes. The filtered product was rapidly cooled on ice. It threw down a copious amorphous deposit, which, when duly washed on the filter with rectified spirit, to free it from adherent carbonate, gave the characteristic reaction of quadri-urate—that is to say, it was decomposed by water with abundant emission of uric acid crystals. A corresponding experiment with a 0·5 per cent. solution of potassium bicarbonate yielded exactly the same results.[1]

We may, therefore, conclude with certainty that when uric acid comes into contact with blood-serum or the standard solvent, it enters into solution in the first instance as a quadri-urate. But the process does not stop here. The quadri-urate gradually takes up an additional atom of base, and is thereby converted into bi-urate; and the bi-urate thus formed is, after some delay, eventually precipitated in the crystalline form.

In order to bring this remarkable succession of events more vividly before your minds I will relate the particulars of four actual experiments.

Experiment 1.—A gram of uric acid was introduced into a flask with 200 cc. of the standard solvent. The flask was tightly corked and placed in the warm chamber, where the temperature was continuously maintained at 100° F. A considerable amount of uric acid went into solution, but a portion remained undissolved at the

[1] Solutions of the common (di-metallic) phosphates of soda and potash, and of the alkaline acetates, also take up uric acid very freely at blood heat; and the combination formed in these cases, in the first instance, is likewise a quadri-urate, as may be shown by the above-described method of cooling on ice.

bottom of the flask, leaving a clear supernatant liquor. Things remained apparently unchanged until the evening of the second day, when a few stars of bi-urate were detected amid the undissolved sediment of uric acid. On the third day, however, a rapid change was observed to be taking place, consisting in an abundant precipitation of stars, and tufts, and detached needles of bi-urate. On the fourth day the precipitation appeared to be nearly complete, for the supernatant liquor now showed only small traces of uric acid when it was treated with hydrochloric acid.

Experiment 2.—A parallel experiment was made with blood-serum. Fresh serum of pig's blood was treated with uric acid in excess in a 4-oz. phial, tightly corked, and chloroformed to prevent decomposition. The phial was gently turned upside down a few times at first, and was not subsequently disturbed; it was then placed in the warm chamber. The serum soon cleared, the surplus uric acid fell to the bottom, and the supernatant serum became transparent. For about twenty-four hours no change occurred, but in the course of the second day stars of bi-urate were detected amid the deposit, and during the third day an abundant precipitation of stars, tufts, and needles of bi-urate took place, exactly resembling those found in gouty concretions (see fig. 3). On the fourth day the process of precipitation was nearly complete, and the supernatant serum was found to be comparatively free from uric acid.

In order to isolate the main part of the process from the initial act of solution the experiments were modified in the following manner.

Experiment 3.—Uric acid in excess was digested, with frequent agitation, in the standard solvent, at 100° F., for twenty minutes. The excess of uric acid was then

filtered off, and the clear solution was placed in a corked phial in the warm chamber. It remained unaltered for two days. On the third day it began to precipitate, and on the fourth day a copious deposition of crystalline bi-urate took place. On the fifth day the process was completed, and the supernatant liquor was found on acidulation to contain only traces of uric acid.

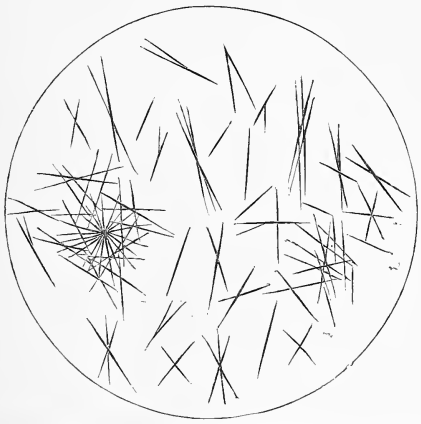

FIG. 3.—Needles, tufts, and stars of sodium bi-urate deposited from blood-serum impregnated with uric acid—identical in appearance with those seen in gouty concretions.

Experiment 4.—Blood-serum of the horse was digested, at 100° F., with excess of uric acid for fifteen minutes with constant agitation. It was then filtered and placed in a corked phial in the warm chamber. In about twelve hours the serum, previously clear, began to lose transparency, and fine needles of bi-urate were detected in it with the microscope. On the next day copious precipitation took place. On the fourth day the process seemed to be completed, and the supernatant serum was found to be comparatively free from uric acid.

It was impossible not to be struck with a certain rough resemblance between the results observed in these experiments and the phenomena of the gouty paroxysm. In the gouty subject it is assumed that the blood becomes more and more impregnated with uric acid until, after a certain period of incubation has been accomplished, sudden precipitation of sodium bi-urate takes place in and about the joints, and the 'fit of the gout' is declared. Then follows a process of recovery, with restoration of the blood to a purer state—that is, with a lessened impregnation of uric acid. In the artificial counterfeit we observe a similar succession of events: firstly, impregnation of the medium with sodium quadri-urate; secondly, a period of incubation or maturation, during which the quadri-urate passes into bi-urate; thirdly, somewhat sudden precipitation of sodium bi-urate in the crystalline form; and lastly, restoration of the medium to comparative purity.

Behaviour of uric acid with synovia.—It is a marked peculiarity of the uratic phenomena of gout that the deposits occur most commonly in and about the joints; and it was a matter of interest in the present inquiry to ascertain how the synovial fluids which bathe these parts behave when impregnated with uric acid; and especially whether these fluids, as compared with blood-serum, and when impregnated to an equal degree, had the property of promoting or retarding the precipitation of bi-urate. This part of the investigation is hampered by the difficulty of obtaining an adequate supply of materials for experiment, and my information thereupon is scanty. The quantity of synovia obtainable from the smaller joints is very minute, even in the case of the large quadrupeds which are dealt with in our slaughter-houses. I have so far only been able to make satisfactory experi-

ments with synovial fluid drawn from the hip of the ox. From this source about a couple of ounces may be obtained from the two joints. Butchers tell me that the synovia from the hip is thinner as well as more abundant than that obtained from the other joints.

On two occasions I was able to examine and compare the synovial fluid of the hip-joint with the blood-serum of the same ox. The behaviour of the two fluids with uric acid was substantially the same; but in both instances I found that, when the media were impregnated with uric acid to an equal degree, precipitation of bi-urate began distinctly a little earlier in the synovia than in the serum. And my impression is, but it is only an impression, that with the thicker and more concentrated synovia of the smaller joints this difference would be more pronounced. Whether there is in this distinction between serum and synovia a key to the preference of uratic deposition for the joints, is a question well worthy of further inquiry. It is at any rate conceivable, supposing the blood and its derivative fluids to be equally impregnated with uric acid, and supposing the synovial fluids to be more largely charged than their congeners with salts, and especially with sodium salts, that precipitation of bi-urate would take place earlier and by preference in and about the joints than elsewhere. This point will be again touched on when I come to speak of the topographical distribution of uratic deposits.

BEHAVIOUR OF THE QUADRI-URATES WITH BLOOD-SERUM AND THE STANDARD SOLVENT.

The quadri-urates behave with the standard solvent and with blood-serum substantially in the same way as uric acid. This might have been expected from the fact

that these media take up uric acid in the first instance as a quadri-urate. There is, however, this difference, that the quadri-urates pass into solution much more rapidly than uric acid; and, consequently, the period of precipitation of bi-urate has its advent considerably accelerated.

GELATINOUS OR HYDRATED MODIFICATIONS OF THE URATES

There is a point of considerable interest in connection with the chemistry of the urates which may be conveniently considered in this place—and that is the occurrence of gelatinous modifications of these compounds, which differ both in physical condition and in solubility from the more common granular and crystalline forms.

The existence of these gelatinous modifications was first noted by Dr. Ord in the course of his well-known researches on the influence of colloids upon crystalline form and cohesion.[1] He observed that when hot saturated solutions of the urates of soda or ammonia were mixed with an equal bulk of strong solutions of the alkaline chlorides or phosphates, the urates were thrown down on cooling in a gelatinous state. Dr. Ord further observed that this condition was not a permanent one; and that the gelatinous matter, after a time, changed into a mass of crystals. The interest for us, in our present inquiry, of these observations lies in the probability that these gelatinous modifications of the urates intervene, perhaps importantly, in the succession of changes which lead up to the formation of uratic deposits in gout. I must, therefore, ask your attention to some additional particulars which I have gathered on this subject.

[1] *On the Influence of Colloids upon Crystalline Form and Cohesion*, by W. M. Ord. London, 1879, pp. 72 *et seq.*

Crystalline sodium bi-urate is very much more soluble, nearly ten times more soluble, in boiling water than in cold water. Nevertheless, such a hot solution, fully saturated, does not deposit its surplus bi-urate on becoming cold; it continues perfectly clear and remains so for a considerable time; the surplus bi-urate is only deposited after the lapse of many days. It is obvious, therefore, that the bi-urate in passing into hot solution undergoes some notable change, whereby its solubility is greatly enhanced. This change consists in the assumption of the gelatinous modification, and herein lies the explanation of the enhanced solubility. These deductions are substantiated by the following experiment. Crystalline sodium bi-urate is dissolved to saturation in boiling water. The filtered solution, when cold, is mixed with an equal volume of a 20 per cent. solution of common salt. A voluminous jelly-like precipitate is thrown down.[1] This is caught on a filter and allowed to drain, and then cautiously washed on the filter with cold water. The gelatinous bi-urate is thus obtained in a condition of approximate purity. Now when this substance is digested at 100° F. with blood-serum, or with the standard solvent, it goes freely into solution—so freely, that when the filtered products are treated with acetic acid they throw down, on standing, a considerable deposit of uric acid. But it has before been shown that these same media, when digested under similar conditions with the crystalline sodium bi-urate, take it up so sparingly that the filtered products do not yield any deposit of uric acid when acidulated.

[1] The gelatinous bi-urates may be thrown out of their solutions in several ways. Instead of common salt a concentrated solution of the phosphate, chloride, or acetate of sodium potassium or ammonium may be used; or any of these salts in crystals may be added to saturation to the solution.

Dr. Ord noticed, as above stated, that the gelatinous bi-urate collected as a mass on a filter passes after a time into the crystalline condition. The same transformation occurs when the gelatinous matter is held in solution in blood-serum or the standard solvent. Such solutions, when set aside, continue clear and unchanged for a certain time, but after the lapse of a day or two the bi-urate is reprecipitated in the crystalline form. The obvious explanation is this. The dissolved gelatinous modification reverts by slow degrees to the anhydrous crystalline condition; and the bi-urate in this condition is, as we know, almost insoluble in these media. Consequently, when the transformation reaches a certain point the bi-urate is necessarily precipitated.

As to the nature of the gelatinous modifications of the urates, Dr. Ord is inclined to regard them as true colloids, and he remarks on their resemblance to the colloidal modification of silica. Their jelly-like appearance is certainly strongly suggestive of this idea. But they differ radically from all true colloids in passing with ease, and unchanged, through the dialyser. Their real nature is, I believe, that of hydrated salts. The crystalline bi-urates are anhydrous; the gelatinous modifications are highly hydrated. It is well known that certain salts can be obtained in several degrees of hydration, and that these several hydrations possess diverse degrees of solubility.

The quadri-urates likewise readily assume the gelatinous modification. Sodium quadri-urate may be obtained in the gelatinous state in the following manner:— A 5 per cent. solution of the common phosphate of soda is heated to boiling with excess of uric acid. The mixture is filtered hot. On cooling the filtrate sets into a jelly. The gelatinous substance thus obtained, pressed

between blotting-paper to deprive it of its mother-liquor, possesses the characteristic reaction of a quadri-urate—that is to say, it is rapidly decomposed by water with copious emission of uric acid crystals.

It was shown in the first lecture that the action of water on the quadri-urates consists in splitting them up into bi-urate and free uric acid. When this reaction is watched under the microscope, as described on pages 7 and 9, the separated bi-urate is never seen in its usual crystalline form, even if the preparation be allowed to completely dry on the microscopical slide. The reason of this appears to be that the bi-urate is liberated in the gelatinous modification, and is, therefore, unrecognisable under the microscope, except as an amorphous matter. I found experimentally that when a quadri-urate in excess is treated with water in a beaker, the supernatant liquid contains the liberated bi-urate in the gelatinous form; and it can be thrown out in this form by adding to the liquid crystals of sodium chloride to saturation.

The gelatinous modifications of the urates, when thrown out of solution as jelly-like masses, appear under the microscope sometimes as amorphous matter, and sometimes as beautiful soft translucent spheres. It may, I think, be inferred that the spheres which constitute the urinary excretion of birds and serpents are first thrown out by the kidneys in this soft translucent condition; and that they acquire the more opaque and harder radiated crystalline structure gradually, as they descend along the lower urinary passages. There would obviously be a mechanical advantage, as regards the delicate exit tubules of the kidneys, for the excretion to be in this soft jelly-like condition while passing through them.

SUMMARY OF THE HISTORY OF URIC ACID IN THE BODY—(*a*) IN THE NORMAL STATE; (*b*) IN THE GOUTY STATE

The facts elicited in this and the preceding lectures enable us to obtain a coherent view of the state and destiny of uric acid in the body. It has been shown that in normal urine uric acid always exists as a quadri-urate; and that in animals which eliminate their nitrogen as uric acid, like birds and serpents, the urinary secretion is composed entirely of the same combination. Proof has also been furnished that in media containing alkaline carbonates—such as the serum of the blood and its derivatives, lymph and synovia—uric acid passes into solution in the first instance as a quadri-urate. From these considerations it may be inferred that in the normal state uric acid is primarily taken up in the system as quadri-urate; that it circulates in the blood as a quadri-urate; and that it is finally voided with the urine as a quadri-urate. In perfect health the elimination of the quadri-urate proceeds with sufficient speed and completeness to prevent any undue detention or any accumulation of it in the blood. But in the gouty state this tranquil process is interrupted, either from defective action of the kidneys, or from excessive introduction of urates into the circulation, and the quadri-urate lingers unduly in the blood, and accumulates therein. The detained quadri-urate, circulating in a medium which is rich in sodium carbonate, gradually takes up an additional atom of base, and is thereby transformed into bi-urate. This transformation alters the physiological problem. The uric acid, or rather a portion of it, circulates no longer as the more soluble and presumably easily secreted quadri-urate, but as bi-urate, which is less soluble, and probably also—either for that

reason or because it is a compound foreign to the normal economy—less easy of removal by the kidneys. The bi-urate thus produced exists at first in the hydrated or gelatinous modification. But with the lapse of time and increasing accumulation it passes on into the almost insoluble anhydrous or crystalline condition; and then precipitation of it becomes imminent, or actually takes place.

THE CONDITIONS WHICH ACCELERATE OR RETARD THE PROCESSES WHICH CULMINATE IN THE PRECIPITATION OF SODIUM BI-URATE

Assuming a real analogy to exist between the processes which go on in serum artificially impregnated with uric acid, and the processes which go on in the blood of a gouty patient, and which culminate in the deposition of uratic concretions, it is a matter of interest, as bearing on the pathology and treatment of gout, to investigate the conditions which, in the artificial parallel, accelerate or retard these processes.

As already explained, these processes consist of three distinct chemical changes. First, the quadri-urate originally formed is converted into hydrated bi-urate; next, the hydrated bi-urate is changed into anhydrous bi-urate; and finally, this anhydrous bi-urate is precipitated in the crystalline form. For the present purpose it will be more convenient to consider these changes as one continuous process, and for the sake of brevity and ease of expression this process may be designated as *maturation*.

The investigation embraced a study of the effects of temperature, percentage of uric acid in solution, and the addition of various saline and other substances to the maturating medium.

(*a*) *Temperature.*—It was found invariably that matu-

ration was more quickly accomplished in the warm chamber at 100° F. than at the temperature of the room, but the ultimate result was exactly the same in both cases. For example, serum charged with 1 part of uric acid in 600 began to precipitate in the warm chamber in four hours, and precipitated copiously in six hours. A duplicate specimen kept at the temperature of the room (65° F.) began to precipitate in eight hours, and did not precipitate copiously for sixteen hours. Another sample of serum, impregnated with 1 part of uric acid in 1,000, began to precipitate in the warm chamber in six hours, and deposited copiously in fourteen hours; while a duplicate kept at the temperature of the room (60° to 70° F.) only began to precipitate in thirty hours, and copious precipitation did not take place for forty-eight hours.

The absolute constancy of these results led to the idea that maturation would go on more rapidly at a febrile temperature (104° to 105° F.) than at the normal temperature of the body, and that herein might be found an explanation of the circumstance that gouty outbreaks sometimes follow immediately on the heels of an injury. When, however, this notion was tested experimentally, no support was found for it.

It was also conceived that although maturation itself was favoured by warmth, the terminal act of the process, namely, the act of precipitation, might, on the contrary (seeing that the bi-urate is more soluble at higher than at lower temperatures), be favoured by cold; and that this might account for the fact that gouty concretions tend to be deposited in the cooler and more exposed parts of the body, in the joints and subcutaneous tissues, rather than in the warmer interior regions. I failed, however, to obtain any direct experimental evidence in favour of this conception.

(*b*) *Quantity of uric acid in solution.*—It was found that no factor exercised so great and decisive an influence on the speed of maturation and the advent of precipitation as the proportion of uric acid in solution. The copiousness of the precipitation was likewise, of course, affected by the same factor. The following experiment with blood-serum, the results of which are arranged in a tabular form, illustrates these points in a striking manner. The phials containing the serum were placed in the warm chamber for fourteen days, and were afterwards kept at the temperature of the room. Chloroform was added to prevent putrefactive changes.

TABLE XVI.—*Showing the Influence of Percentage of Uric Acid in the Medium on the Speed of Maturation, and the time of Advent of Precipitation.*

Quantity of uric acid contained in the serum	Time of precipitation of sodium bi-urate
1 in 1,000	Precipitation began in six hours, copious precipitation in fourteen hours
1 in 2,000	Precipitation began in thirty-three hours, copious precipitation in three days
1 in 3,000	Slight precipitation began in three days, which became a little more copious in twelve days
1 in 4,000	A few needles of bi-urate were detected on the sixth day; more needles and a few tufts in twelve days
1 in 5,000	A few short needles were detected on the thirteenth day. In thirty days the needles were somewhat more numerous
1 in 6,000	No needles were discoverable in fourteen days; a few were detected in forty days
1 in 8,000	No needles could be detected after the lapse of forty days

Assuming that the inflammatory arthritic attacks in gout are directly due to copious and sudden precipitation of crystalline stars and needles of sodic bi-urate in the

cartilages and fibrous structures of the joints, the evidence before me indicates that such copious sudden precipitation can only take place when the fluids bathing hese structures are impregnated with uric acid in at least the proportion of 1 part in 2,500. Below this point the precipitation occurs slowly and scantily, and only in the form of short scattered needles. When the proportion of uric acid in the serum was only 1 part in 5,000, the deposited needles were mostly about as long as the diameter of a red blood-disc, some were twice this length, and a few three times this length, and all were of extreme tenuity. It is quite conceivable that this slighter precipitation in the tissues of short scattered needles might account for certain irritations in the various organs, such as characterise irregular or larval gout, but it could scarcely engender downright inflammatory attacks. It is further conceivable that the presence in the blood of such scattered needles might constitute foci, around which clotting might take place; and that the thrombosis not unfrequently observed in gouty cases might thus be accounted for.

The impregnation of the blood in gouty persons with uric acid to the extent of these lesser degrees is within the range of observed actualities. Sir Alfred Garrod obtained, by quantitative analysis, from the blood-serum of one of his patients uric acid to the amount of 1 part in 5,714; and he remarks that the quantities thus recoverable from the blood are probably much under the actual amounts, as considerable loss is liable to occur from unavoidable causes.

These considerations lead to the suggestion that a microscopical examination of the blood in gouty persons might sometimes reveal the existence of needles of bi-urate in that fluid. I tested this point in ten cases

of chronic gout by examining a drop of blood drawn from the finger, but I failed to obtain positive results.

(*c*) *Influence of saline substances.*—The effect of saline substances on the maturating process was tested by adding small quantities of various salts to serum impregnated with uric acid, and observing whether these additions accelerated or retarded precipitation. The experiments were carried out in the following manner. Uric acid was dissolved at blood heat in blood-serum in the proportion of 1 per 1,000 or 1 per 2,000. A number of phials capable of holding 25 cc. were charged with the serum thus impregnated. One phial had no further addition made to it—this was the control phial. To the others, small quantities, varying from 0·05 per cent. to 0·2 per cent. of the salts to be tested, were added. The phials were then chloroformed to prevent decomposition, and placed in the warm chamber. The occurrence of precipitation was noted at two points, first, at its very onset, as revealed by the detection on microscopical examination of needles of bi-urate; and second, when precipitation became copious and was recognisable by the naked eye.

A large number of experiments were made on this plan.

The state of the medium during precipitation was that of a supersaturated solution; and consequently, a very slight, often inappreciable, inequality in the conditions of the experiment was sufficient to disturb the time and rate of precipitation. For this reason it was frequently found necessary to repeat the observations once and again to get the correct indication. I need not trouble you with details; the following summary indicates sufficiently the conclusions deduced from the experiments.

The addition of *sodium* salts to the maturating medium hastened precipitation. An idea of the degree

of acceleration may be gathered from the following examples. Serum impregnated with uric acid to the extent of 1 part per 1,000 commenced to precipitate in seven hours, and precipitated copiously in sixteen hours. A parallel experiment, in which 0·2 per cent. of sodium chloride had been added to the serum, began to precipitate in five hours, and precipitated copiously in twelve hours. Another sample of serum was impregnated with uric acid to the extent of 1 part in 2,000. This began to deposit crystals in thirty hours, and deposited freely in ninety-six hours. In a parallel experiment, in which 0·2 per cent. of sodium bicarbonate had been added to the medium, precipitation began in twenty hours, and free precipitation took place in forty hours. The alkaline reacting salts—the carbonate and phosphate—had exactly the same effect as the chloride and sulphate, which are neutral in reaction.

The addition of *potassium* salts sensibly retarded precipitation, but did not appreciably diminish the eventual amount of it. Here, again, the carbonate and phosphate, which are alkaline, produced just the same effects as the chloride, iodide, and bromide, which are neutral. Both with potassium and sodium salts the results were entirely dominated by the nature and quantity of the bases added, and had no reference to the acidulous radicle with which the bases were combined.

The addition of *calcium* and *magnesium* salts appeared to delay precipitation, but their action in this respect was quite insignificant, or even doubtful.

The salts of *lithium* had not the slightest influence either way.

Piperazine, whether in the free state or as chloride, exercised no influence on the advent of precipitation.

LECTURE IV

CHEMISTRY OF URATIC PRECIPITATION CONTINUED—BEARING OF THE INVESTIGATION ON THE THERAPEUTICS OF GOUT

TOPOGRAPHY OF URATIC DEPOSITS

Mr. President and Gentlemen,—The topographical distribution of uratic deposits through the various organs and tissues of the body exhibits certain well-marked characteristics. These deposits are found almost exclusively in structures belonging to the connective tissue class—in cartilages, ligaments, tendons, and other fibrous structures, and in the cutaneous and subcutaneous connective tissues. On the other hand, uratic deposits are conspicuously absent from the muscular tissue, and from the substance of the brain, liver, spleen, and lungs.[1] The tissues which are liable to uratic precipitations are, however, not equally so in the different parts of the body. The cartilages, ligaments and tendons in and about the joints which are bathed with synovia are much more obnoxious to these deposits than are cartilages and fibrous structures situated at a distance from joints, and which are not bathed with synovial fluid. It is further to be noted

[1] Uratic concretions are frequent in the kidneys, but the relation of these organs to the excretion of uric acid gives them a special position in regard to this point.

that uratic deposits favour the more superficial and cooler parts of the body, especially the upper and lower extremities, and are more rare in the deeper and warmer interior parts of the trunk. It may be inferred from these particulars that the influences which co-operate to determine the site of uratic precipitations are of several and quite different kinds. I do not propose to discuss this subject comprehensively, but to refer only to two points which seem capable of a chemical or physical elucidation. These are, the influence of the proportion of sodium salts in the several organs and tissues, and the influence of synovia.

(*a*) *Influence of the proportion of sodium salts.*—We have seen that the dominant factors in uratic precipitation, as studied in the laboratory, are the proportion of urates and the proportion of sodium salts contained in the medium.[1] The highest tendency to precipitation is reached when there is a concurrence of these two factors in maximum intensity. A medium may be rich in urates, but if it be, at the same time, poor in sodium salts, its tendency to precipitation is feeble—and *vice versâ*. This fact has a direct bearing on the topography of uratic deposits. For supposing the system of a gouty man, on the eve of an outbreak, to be throughout equally impregnated with urates, it is obvious, from the experimental evidence before adduced, that uratic precipitation would take place earliest, and most copiously, in those parts which were richest in sodium salts, and take place latest, or not at all, in those parts which were poorest in sodium salts. Let us now examine the distribution of sodium salts in the body, and seek to

[1] The proportion of calcium and magnesium salts is always too small to have any appreciable influence on the occurrence of uratic precipitation.

ascertain if there be any correspondence between the liability to uratic deposits in the several tissues and organs, and the proportion of sodium salts contained in them. In the subjoined table I have arranged the results of analyses on this point. The materials available for comparison are not so full and precise as could be desired, but their general significance is, I think, quite unmistakable. In order to render the comparison more complete and instructive, I have included in the table not only the results with respect to the solid organs and tissues, but also those with respect to blood-serum and its derivatives, lymph and synovia.

TABLE XVII.—*Showing the Percentage of Sodium Salts in the several Fluids, Tissues, and Organs of the Body.*[1]

	Per cent.		Per cent.
Blood-serum . .	0·70	Blood-corpuscles . .	0·20
Lymph . . .	0·70	Brain	0·20
Synovia . . .	0·80	Muscle . . .	0·08
Cartilage . . .	0·90	Spleen . . .	0·04
Fibrous tissue . .	0·70	Liver	0·02

An inspection of the table shows that the tissues which are liable to uratic deposits are very much richer in sodium salts than the tissues and organs which are not thus liable. The remarkable immunity from uratic deposits enjoyed by the muscular tissue, by the brain, liver, and spleen, may be inferred to be due, for the greater part at least, to their poverty in sodium salts. Turning to Table XIII. p. 79, we see that the solvent

[1] The figures in this table are to be taken as approximative numbers. Most of them are deduced from analyses cited in Gamgee's *Physiological Chemistry*. The figures for synovia and fibrous tissue are deduced from the author's own analyses of the synovial fluid and tendons of the ox, the amounts being reckoned as chlorides. A more recent analysis of human lymph by Munk and Rosenstein (*Maly's Jahresbericht*, Bd. xx. p. 40) gives the sodium salts as 0·80 per cent.

power of a medium for sodium bi-urate increases in correspondence with its lessening proportion of sodium salts. Brain has only about one-fourth the percentage of these salts as compared with cartilage and fibrous tissue, and muscle only one-tenth. This difference signifies (roughly) that brain has four times more power, and muscle ten times more power, of dissolving sodium bi-urate than cartilage and fibrous tissue, and therefore, respectively, four and ten times more power of resisting its precipitation in their substance. It might probably be truthfully said, on this ground, that brain, muscle, liver, and spleen could not become the sites of uratic deposits until the connective tissues had been in this respect exhausted. It is true that the immune tissues and organs have a quicker circulation than cartilages and tendons, and this doubtless contributes importantly to the difference; but it scarcely fully accounts for it, otherwise we should expect that the skin, which is abundantly supplied with blood-vessels, would share this immunity. The prepotency of the cartilages and fibrous tissues to induce uratic precipitation must obviously operate in a conservative direction, and serve to protect the more vital organs of the gouty from similar precipitations, where they would produce more deadly effects.

(*b*) *Influence of synovia.*—The connection between synovia and gouty deposits is evidently very close and special. Synovial fluid has itself been repeatedly found heavily laden with crystals of sodium bi-urate. In the great majority of the less severe cases of gout the deposits are exclusively confined to those cartilages, ligaments, and tendons which are in actual contact with synovial sacs or synovial sheaths. With regard to the articular cartilages it may, I think, be demon-

strated that the uratic precipitation actually takes place *from* the synovial fluid, and is not self-originating in the cartilaginous substance. Vertical sections of gouty cartilages are very convincing on this point. If such sections are examined under the microscope, it is seen that the deposit hugs the synovial surface of the cartilage, and that it becomes progressively sparser and sparser towards the deeper layers—the central and deepest parts being often quite free from deposit.

This mode of distribution, moreover, implies that the process of deposition, so far as concerns the cartilage, is a purely passive and physical one, and nowise active and vital in its initiation. We may suppose that the urate dissolved in the synovia penetrates by liquid diffusion into the superficial layers of the underlying cartilage, and that when the critical moment arrives precipitation takes place simultaneously in the synovia and in the cartilage. On this view the after-consequences are entirely secondary, and are due to the reaction of the tissue against the presence of a foreign body lodged in its substance. It may interest you to know that this process can be artificially imitated in the laboratory, and that a counterfeit gouty joint can be produced in the articulation of a dead animal. I here show you samples of such counterfeits; they were prepared in the following manner. Tarsal bones of a pig were suspended in wide-mouthed phials, charged with a saturated solution of sodium bi-urate made in hot water, and then cooled. The phials were chloroformed and corked, and then set aside in the warm chamber, or at the temperature of the room. Reprecipitation of the bi-urate takes place in two or three days. If the bones are now examined, the articulating ends are found to be encrusted with a chalky matter, which cannot be wiped off with a towel nor

removed with a nail brush. They present an exquisite imitation of the plastered appearance of a gouty cartilage. If vertical sections of such cartilages (previously hardened in absolute alcohol) are made, and examined with the microscope, the deposit is seen to be situated in the substance of the tissue, close beneath the synovial surface of the cartilage, and to be composed of a dense felt of fine needles of bi-urate. The deeper layers of the cartilage are not affected. It may be inferred that the deposits which occur in the ligamentous and tendinous structures of gouty joints are produced in the same way as those found in the cartilages; and that the precipitations take place, chiefly at least, from the synovial fluid bathing them, and that they are not due to primary morbid changes in the structure of the tissues.

Two questions may now be asked:—First, why does gouty precipitation take place preferentially in synovia rather than in its cognates, the serum of the blood and lymph? And second, why do the joints differ so much from each other in their liability to attack? I will discuss the two questions together, as the arguments often dovetail into each other. It may be that there is, as Sir A. Garrod suggests, some special attraction in the joints for uric acid. But there are undoubtedly other factors which come into play. Synovia is a comparatively motionless fluid, while serum and lymph are in ceaseless motion. And as a still pool crystallises into ice sooner than a running brook, so likewise—supposing serum, lymph, and synovia to be equally impregnated with urates and sodium salts—the tranquillity prevailing within the synovial cysts would give to synovia a priority in uratic precipitation over the restless blood-serum and lymph. Then as regards the varying liability of the different joints to gouty attacks, it may be pointed out

that the synovial pouches and sheaths are shut sacs, standing apart from each other, and isolated from the general panmixia of the circulation. It might consequently be expected—indeed, it is an observed fact—that the synovial fluids in different joints should present differences in the relative proportion in their constituents. Some are certainly more concentrated than others ; and we can easily believe that they are not quite identical in their degree of impregnation with urates and with sodium salts. In this way the several joints might come to vary considerably in their liability to uratic precipitation.

Frerichs has contributed some interesting particulars on synovia in animals.[1] His observations indicate that synovia varies both in quantity and quality under different modes of life. He found that stall-fed horses and oxen, leading an idle existence, had twice as much synovia in their joints as similar animals roaming in the meadows, or doing work. Moreover, the composition of the fluid varied in the two cases. In the idle animals the synovia was more watery, and contained less albuminoid matters, but—and this is significant—a larger proportion of mineral salts, which consist almost entirely of sodium salts. We might conjecture from this fact, that if horses and oxen were liable to uratic precipitations, the idle stall-fed animals would be more subject to such deposits than the same animals leading a more active life. Perhaps we may discern herein one reason why men who lead a sedentary life are more subject to gouty deposits than men who take active exercise.[2]

[1] R. Wagner's *Handwörterbuch d. Physiol.*, Bd. iii. Pt. 1, p. 463.

[2] A plausible way of explaining the sudden onset of gouty paroxysms is to assume a rapid dehydration of the contents of the synovial sacs. Withdrawal of water from synovia, if it were already pretty fully charged with urates, would at once bring it to the critical point of pre-

Interpretation of the appearances found at the necropsy of gouty subjects. Re-solution of gouty deposits.—Before leaving the subject of the topographical distribution of gouty deposits, I should like to say a word on the need of caution in interpreting the appearances, both positive and negative, observed at the necropsy of gouty subjects. The incidents of the gouty diathesis, especially in the earlier periods, pursue a markedly interrupted course. Long intervals of months or years often elapse between the arthritic outbreaks. During these intervals the blood of the gouty man recovers its purity more or less completely; and approximates in its content of uric acid to the blood of a healthy person. The solvent relation of the bodily fluids to the material of gouty deposits is simply a question of saturation or sub-saturation. If the lymph or synovia at a certain spot become saturated, or rather supersaturated, with sodium bi-urate, precipitation of that substance will inevitably take place into the contiguous fibrous tissues. And if, after such an event, the lymph or synovia recover its purity and become approximately free from bi-urate, as in due course usually comes about, a process of slow re-solution will of

cipitation. This would operate with double force, by increasing the percentage both of the urates and of the sodium salts in the medium. Thus the two dominant factors in uratic precipitation would be brought into concurrent and intensified action. This explanation might apply to two classes of cases. It is well known that gouty persons sometimes experience an arthritic attack immediately after a luxurious meal with free wine drinking. It does not seem improbable that the effect of such an indulgence would be to induce a temporary concentration of the synovial fluids, and the drouth which follows is strongly suggestive of a certain dehydration of the tissues. It is also conceivable, in those instances where a trifling injury to a joint provokes a gouty seizure, that the initial local effect was a dehydration of the synovial secretion—just as the first incident of a cold in the head is a drying of the nasal passages.

necessity set in. For, as has been before demonstrated, sodium bi-urate, although very sparingly soluble, is by no means insoluble in these media. The rate and amount of re-solution of uratic deposits must necessarily vary greatly in different cases, according to the degree of sub-saturation attained by the bodily fluids, the massiveness and penetrability of the deposits, and the length of time during which the favourable conditions endure.

If regard be had to the often long survivorship of gouty persons, and the interrupted course of the arthritic incidents, it seems highly probable, in the lapse of a long life, that deposition and re-solution of uratic matter may take place once and again in a gouty joint. There are undoubted instances, of which Sir Dyce Duckworth [1] records one observed by himself, where no uratic concretions have been found after death in joints which had, at some previous period, undergone typical gouty attacks. The presumption in such a case is, not that deposits never existed, but that they had been re-dissolved in the intervals of amendment. Uratic concretions in the pinna of the ear have sometimes been actually observed to come and go, and come again. There is no reason why the same thing should not occur within the joints; and such vanished concretions might leave behind them permanent changes in the cartilages and bony structures as tell-tale evidence of their former presence. On the other hand, the discovery after death of uratic deposits in a joint is not always to be regarded as a certain proof that the joint had passed through an inflammatory gouty attack. The observations of Moxon and Fagge seem to warrant this conclusion; and they reasonably suggest that when the precipitation of the urates takes place

[1] *Treatise on Gout*, by Sir Dyce Duckworth, p. 68.

slowly and by degrees, there may be no accompanying inflammatory outbreak to mark the event.[1]

The experimental evidence before adduced indicates that when lymph or synovia is impregnated with sodium bi-urate to or above 1 part in 6,000, the medium is supersaturated, and precipitation either actually occurs or is impending. On the other hand, when these fluids contain less bi-urate than 1 part in 10,000, the medium is under-saturated, and there resides in it a certain power of re-dissolving uratic deposits; and, of course, the nearer the medium is to freedom from urates, the higher rises this solvent power. It may, further, be inferred that the solvent action will be most effective in the case of deposits situated in textures like the fibrous tissues which have a comparatively free lymph flow, and, conversely, that it will be least effective in textures, like the cartilages, which have a sluggish lymph flow. This is probably the reason, or chief reason, why the cartilages figure more prominently than the fibrous structures in the morbid anatomy of old gouty joints. Probably both tissues were originally infiltrated with bi-urate crystals in equal degrees; but the fibrous structures afford greater facilities for their re-solution in the periods of amendment than the cartilages, and hence the greater persistence of the deposits in the latter tissue.

THE MODE IN WHICH URIC ACID PRODUCES ITS INJURIOUS EFFECTS

A problem of great interest in regard to the elucidation of gouty manifestations is the mode or modes in which uric acid produces its injurious effects. The main question is, whether these effects are exclusively due

[1] Fagge and Pye-Smith's *Handbook of Medicine*, p. 674.

to the *mechanical damage* consequent on its precipitation as sodium bi-urate in the tissues; or whether, in addition, uric acid circulating in the blood in a state of solution is capable of acting as a *true poison*.

With regard to the incidents of regular gout, the mechanical theory seems to offer a natural and complete explanation. The crystalline urates precipitated in the cartilaginous and fibrous structures of the joints necessarily act as foreign bodies; they excite irritation, clog the lymph channels, exercise pressure on the tissue elements, and impede their nutritive operations. These effects sufficiently account for the inflammation, pain, and swelling which ensue, and explain the remoter degenerative changes which follow after. Nor need we look beyond physical conditions to account for the diversity witnessed in the local manifestations. It is easy to understand that depositions occurring within the tense unyielding structures of the joints would produce widely different results from similar depositions in the loose subcutaneous tissue, or in the rim of the ear. It is equally easy to understand that the suddenness or slowness of the precipitation, its copiousness or scantiness, would necessarily cause great variation in the intensity and character of the local disturbances. So easy and natural is this explanation, that we might even predicate, from our general knowledge of pathological cause and effect, that if similar depositions of crystals of carbonate of lime, or of any other inert substance, were to take place in the same localities, there would follow very much the same train of morbid sequences as are witnessed in connection with uratic precipitations.

It is in the explanation of the phenomena of irregular gout that the mechanical theory of the action of uric acid seems inadequate; and it is to meet this lack that

the theory of a poisonous action has been set up, and is invoked. The visceral disturbances and manifold neuroses which trouble the gouty have not yet been anatomically traced to uratic precipitation, and there seemed no other way of explaining their occurrence—if they were to be linked with uric acid at all—except by assuming that uric acid was possessed of toxic properties. The acceptance of this view appears to me on several grounds to be extremely difficult.

There is, first, the complete absence of direct experimental proof. Animals have been made to ingest large quantities of uric acid with their food, and urates in solution have been freely injected into their veins, without eliciting any signs of poisoning.

In the next place, the idea that uric acid is poisonous seems opposed to broad biological analogies. Uric acid is the physiological homologue of urea; each of these bodies constitutes, in its separate domain, the final term of nitrogenous metabolism. It cannot be said, without an abuse of terms, that urea is a poisonous substance;[1] and it would be strange if its homologue, uric acid, differed from it in so important a particular as the possession of toxic properties.

The theory appears not less improbable when examined from a nearer point of view. The system of the gouty man is at times surcharged with uric acid. On the eve of an outbreak, the fluids of his body, in parts

[1] The word poisonous is here used with its ordinary meaning. Almost any substance which could be got into solution in the blood in very large quantities would produce deleterious effects, even common salt. Urea can be taken into the stomach in drachm doses without harm; and Dr. Rose Bradford, who has paid particular attention to this point, informs me that the human body contains habitually in the normal state some 30 to 45 grains of urea, and may contain very much larger quantities than this, without provoking any signs of poisoning.

at least, must be impregnated with bi-urates to saturation; for, of course, no precipitation can occur until this point is reached. Yet, with fluids thus saturated with urates, such persons often betray not the slightest sign of poisoning, and enjoy complete immunity from symptoms of every kind until overtaken unwarned by the sudden precipitation which provokes the arthritic attack.

Again, the manifestations of irregular gout are so extremely diverse in seat and character that it is hard to believe that they can be produced by one and the same toxic agent. Sometimes they implicate the stomach, sometimes the liver, or heart, or lungs, and, oftenest of all, the nervous system. This diversity is, however, easily explicable on the supposition that the disturbances are caused, not by uric acid in a state of solution acting as a poison, but are really due, like the arthritic manifestations, to uratic deposition; that is to say, to actual precipitation of crystals of bi-urate into the connective and fibrous structures of the implicated organs, or into the fibrous sheaths of the nerves which control their functions. Observations at the bedside and in the dead-room lead to the inference that uratic precipitation is very variable in its mode and incidence. In certain conditions the crystals appear to descend in sudden and copious showers, which provoke a sharp inflammatory reaction, as in the regular arthritic seizures. In other conditions the crystals seem to fall in gentle sprinklings, sufficient perhaps to cause irritation, if the implicated tissue be a sensitive one, but not enough to cause downright inflammation. The peculiar pricking pains in the joints, which some gouty persons invariably experience after partaking of certain wines, are highly suggestive of the occurrence of these slighter precipita-

tions. Now if these slighter precipitations, instead of falling on the joints, fell upon the membranes of the brain or upon the fibrous sheaths of the nerve-roots, this would, I submit, afford an adequate explanation of the phenomena of irregular gout. Of course it may be objected that no such slight precipitations have actually been found. But have they been looked for? Has the microscope been used in the investigation? In prosecuting such a search it would have to be borne in mind that precipitations of the kind supposed would be apt to be fugitive, and that negative results would have to be interpreted with caution. For it is obvious, in the case supposed, that when the stress of saturation of the fluids with urates was relaxed, and the blood again recovered its power of dissolving these compounds, these slight deposits would be speedily removed by re-solution, and not a trace of them might remain at the autopsy.

We scarcely realise how imminent a slight but widespread precipitation of the crystalline bi-urate must not infrequently be in the gouty system—involving the blood and lymph, as well as the fibrous tissues throughout the body. It has been already shown that when the serum of the blood is impregnated with sodium bi-urate to the extent of 1 part in 6,000, supersaturation is attained; and precipitation is then, of course, imminent. On the other hand, Sir A. Garrod has proved by quantitative analysis that the blood-serum of the gouty man is sometimes actually impregnated with uric acid to this extent. These two facts taken together indicate that the explanation here suggested of the phenomena of irregular gout stands on a strong basis of *a priori* probability—and thus dispenses with the necessity of assuming that uric acid and its compounds are endowed with poisonous qualities.

This mode of viewing the subject enables us to bring the diverse morbid effects of uric acid into uniform line. Uric acid and its compounds are deleterious simply because of their sparing solubility in the bodily media. It may be said that the final cause of uric acid gravel is the sparing solubility of free uric acid in urine; and, in like manner, it may be said that the final cause of gouty precipitations is the sparing solubility of sodium bi-urate in blood-serum, lymph, and synovia.

Ebstein's theory.—Professor Ebstein[1] has formulated an entirely new theory of the gouty process; and he has adduced in its support a considerable amount of experimental and other evidence. His researches have attracted a good deal of attention, both in this country and elsewhere—his work on the subject has been translated into French, and has received the imprimatur of Professor Charcot. This theory involves several questions relating to the chemistry of gout, and contains assumptions and explanations which are traversed by the results of the foregoing inquiry.

The theory sets out with the assumption that the initial step in the gouty process consists in the infiltration of the tissue, in circumscribed areas, with neutral urate of soda in the liquid form. The neutral urate, according to Ebstein, acts as a chemical irritant on the implicated tissue, like a drop of acid or a drop of alkali, and provokes therein what he terms necrotising processes, which ultimately lead to complete necrosis of the tissue in the affected areas. These areas of necrotising and necrotic processes act as foci of reactive irritation on the surrounding parts, and thus produce, and explain, the inflammatory incidents of gout. The deposition of urates in the crystalline form, according to the same authority, occurs exclusively in the fully necrosed areas, and is not a primary but a secondary event. To account for the

[1] *Die Natur und Behandlung der Gicht*, by W. Ebstein, Wiesbaden, 1882.

formation of the crystalline urates at these spots, Ebstein invokes the aid of a hypothetical acid, generated in the necrotic areas, which transforms the infiltrating neutral urate into the crystalline bi-urate.

There are several difficulties in the way of accepting this theory. In the first place, there is not, as I have before pointed out, any evidence that the neutral urate ever exists, or can exist, in the living body; uric acid is not primarily taken up by the blood and lymph as a neutral urate, but as a quadri-urate. It has also been proved that the formation and deposition of the crystalline bi-urate are not favoured by the intervention of an acid and a diminution of the alkalescence of the medium. Ebstein is very positive that the crystalline urates are only deposited in tissue which has already undergone necrotising and necrotic changes; and he states that he has never seen such deposits in articular cartilages, except in areas where the tissue had undergone complete necrosis. This is, however, not the experience of other observers. Sir A. Garrod, Cornil, and Ranvier, and Sir Dyce Duckworth, have described and figured deposits of the crystalline urates in portions of cartilage which were either uninjured or only slightly injured, and certainly not necrosed, at the site of the deposits. I have myself made and examined a good many sections of gouty cartilages with reference to this point, and I can fully endorse the following statement by Sir Dyce Duckworth: 'The appearances afforded by study of sections of cartilages so infiltrated justify the opinion that the deposit, in crystallising, pushes its way without special regard to the component elements of the tissue, and acts in respect of it as if it were an indifferent or homogeneous medium.[1]

The destructive changes seen in certain portions of gouty cartilages where the deposit is dense, or may be assumed to have been dense at some previous period, are much more naturally explained as the direct result of the pressure of the felted masses of crystals on the tissue elements, and as the sequelæ of the inflammatory and degenerative processes

[1] *Treatise on Gout*, by Sir Dyce Duckworth, p. 64.

set up by their presence. It has been noted that crystalline urates are sometimes found floating free in the synovial fluids of gouty joints; it will scarcely be contended that necrotising and necrotic processes can take place in synovia! We have also seen that close imitations of uratic deposits in gouty cartilages can be produced in the articulations of a dead animal—and therefore, of course, without the intervention of any pathological processes.

But Professor Ebstein chiefly relies for the substantiation of his theory on the experimental evidence which he thinks he has obtained, that uric acid and its compounds are capable of acting as chemical irritants on the tissues, and of thus engendering the necrotising and necrotic changes above mentioned. He pursued two lines of investigation on this point. The first consisted in injecting into the cornea of a rabbit a solution of uric acid in phosphate of soda. This was prepared by heating uric acid to saturation in a five per cent. solution of sodic phosphate, and filtering the product when it had cooled down to the temperature of the body.[1] When this solution was injected warm into the cornea there followed changes of an inflammatory character, which Ebstein attributed to the irritant effect of the urate in solution on the corneal tissue. There is, however, here a source of fallacy. The solution used is very rich in urate; so rich that in three or four hours, even when maintained at the heat of the body, it begins to precipitate the contained urate in the gelatinous form, and soon becomes almost a solid jelly. So that what probably occurred was this: Three or four hours after the injection was made into the cornea, the tissue of the affected area became infiltrated with a thick

[1] The instructions for the preparation of this solution are taken from the French translation—as representing, presumably, the latest revision of the author's procedures. Those given in the German edition direct that the filtration should be accomplished, not at blood heat, but when the solution becomes cold. The discrepancy is no doubt due to inadvertence; but it makes an immense difference in the strength of the solution whether it is filtered at blood heat or is filtered cold. In the former case the filtrate is very rich in urate, in the latter case it contains very little.

gelatinous matter, which would, of course, act as an obstruent, and mechanically (not chemically) excite irritation.[1]

The second line of investigation consisted in a study of the uratic deposits which are formed in fowls when the ureters are ligatured, or when the kidneys are progressively disabled by repeated injections of chromate of potash. It is, however, very doubtful whether the processes which Professor Ebstein had under his eyes in these experiments are really parallel with those occurring in human gout. The production of uric acid in the bird is so enormous that, when the means of exit by the kidneys are impeded, there is a rapid accumulation of it in the tissues, probably first in a state of solution as quadri-urate, then precipitated in the tissues as gelatinous bi-urate, which in its turn is afterwards changed into crystalline bi-urate. This is, I infer, the series of changes which Ebstein witnessed in the liver and muscular tissues of the birds he operated upon.[2] In man and mammals the production of uric acid is all too small to furnish, under any circumstances, a solution sufficiently concentrated to throw down the urate in the gelatinous form. In all my experiments on the behaviour of uric acid with blood-serum and synovia, I have never seen the least indication of precipitation, except of the far less soluble crystalline bi-urate.

[1] Ebstein varied the experiment by injecting into the cornea uric acid in powder suspended in water, and he controlled this experiment by making similar injections with magnesia suspended in water. But it is obvious that the two cases are not parallel. The interstitial juices of the cornea are alkaline; and uric acid is freely soluble in such media. Magnesia, on the other hand, is insoluble in such media, and its behaviour therein would consequently be different.

[2] The fact that the uratic deposits studied by Ebstein in his experiments on fowls were situated in the liver and muscular tissue, where uratic deposits do not occur in human gout, is a pretty strong indication that the two processes are in some particulars radically unlike.

BEARINGS OF THE INVESTIGATION ON THE THERAPEUTICS OF GOUT

In dealing with the therapeutics of gout I shall confine myself to those points which have a chemical bearing, and which can be brought into touch with the results of the foregoing investigation. According to the views developed in these lectures, the mischief done by uric acid in gout is contingent on its precipitation as crystalline biurate in the tissues or in the fluids of the body. Within this limited scope the study of the treatment of gout resolves itself into a study of the means we possess of controlling the factors which promote or hinder this precipitation.

The nature of the primary error which predisposes to uratic precipitation has been much debated. The most defensible view is in the direction indicated by Sir Alfred Garrod, that it consists in a defective capacity in the kidneys for the excretion of uric acid. This view does not imply the existence of a general renal inadequacy, but a special inadequacy with regard to this particular point. The way in which such a special inadequacy can arise in individuals and families is a matter of speculation. Physiologists tell us that the separation of uric acid and urea by the kidneys is not a mere act of filtration, but an act of genuine secretion by cell-agency. In a previous lecture I advanced some considerations in favour of the conception that the presence of uric acid in mammalian urine might be regarded as a vestigial phenomenon—connoting the evolution of the mammal from an ancestor which eliminated its nitrogen as uric acid. In the course of such an evolution a double change would be in progress; namely, a gradual substitution of urea for uric acid as the final term of

proteid metabolism; and a complementary modification in the functional aptitudes of the renal cells—that is to say, an ever-increasing aptitude for the excretion of urea and an ever-diminishing aptitude for the excretion of uric acid. When, after long æons, the mammalian type was at length evolved, there remained only a small residuum of uric acid to be dealt with; and, correspondingly, only a small residuum of the original aptitude of the renal cells for its excretion. A feature thus begotten would, of course, like other residuary features, present great variation in different individuals. Pushing the speculation a step further, we seem to get a glimpse of a possible explanation of the origin of the gouty habit in the individual and of the associated tendency to uratic depositions. Generators of gout and members of gouty families are, for the most part, people of fine frames and ample appetites, who are withal great consumers of nitrogenised food. In such persons there is an enhanced production of urea, which expands by grams, while uric acid only expands by grains.[1] There would thus arise a persistent demand on the urea-excreting faculty, which could only be satisfied by an encroachment on the residuary faculty for the excretion of uric acid. And thus there would be established, in the course of time, a dangerously narrow range of adjustment between the quantity of urate thrown into the circulation and the capacity of the kidneys for its elimination.

A defective and restricted power in the kidneys for the excretion of uric acid, whether brought about in the manner above suggested or in some other way, as by lead poisoning, or by a premature senescence of the renal cells, would obviously operate to foster a tendency to uratic precipitation. For if the daily quantum of

[1] Neubauer and Vogel's *Analyse des Harns*, 9th Ed. Part II. p. 239.

uric acid produced exceeded the quantum which the kidneys were capable of removing, were it only by half a grain per day, urates would inevitably accumulate gradually in the blood, and their precipitation would necessarily at length become imminent.

It is a matter of daily observation that the tendency to uratic precipitation in gouty persons varies in intensity through all degrees; and it is important to bear this in mind in assessing the value of remedial measures. In some cases the tendency is inveterate; the capacity of the kidneys to remove uric acid habitually falls short of the quantity which requires removal; and we are obliged to recognise the existence of a standing arrearage in this item of the renal functions. In such a state of things it is vain to expect that we can redress the balance, and restore the equilibrium between production and elimination. Frequently recurring uratic precipitations into the fibrous structures are inevitable. Indeed, it may be held that such precipitations are to be desired, as affording a provision for the immediate safety of the individual; for if they did not take place into these less highly organised tissues, they might occur in more vital situations—in the brain or liver, or throughout the mass of the blood itself. In other, and fortunately more numerous, cases the deficit is slight or occasional; and precipitation is almost reduced to the significance of a mischance or accident. In these cases it is possible, as experience has amply proved, by patient persistence with remedial measures, either to re-establish the desired equilibrium, and prevent precipitation; or to lengthen the intervals between the attacks and lessen their severity.

I now proceed to the consideration of the means we possess of influencing the factors which control the precipitation of sodium bi-urate in the body, and help or

hinder the formation of gouty deposits. These means may be divided into those which belong to the domain of diet and regimen, and those which consist in the administration of medicinal substances.

(*a*) DIET AND REGIMEN

Restricting the production of uric acid.—It has been shown that one of the main factors in determining uratic precipitation is the percentage of urates in the medium. Other things being equal, the larger the proportion of urates present, the earlier and more abundant is the deposition of the crystalline bi-urate. Our power of controlling this factor lies almost entirely in the direction of regulating the diet. Numerous series of experiments have been made on the effect of diverse kinds of food on the production and excretion of uric acid. The chief point of therapeutical interest that has been clearly made out is this: that the ingestion of large quantities of proteid matter is attended with an increased production of uric acid—and *vice versâ*. It does not appear clear that proteid substances derived from the Animal Kingdom differ in this respect from those derived from the Vegetable Kingdom. But inasmuch as the commonly-used articles of food of animal origin—such as butcher's meat, poultry, game, fish, eggs, and cheese—are richer in proteid stuff than the commonly-used articles of vegetable origin—such as bread, oatmeal, rice, potatoes, and garden products—it is true that a vegetable diet is less productive of uric acid than an animal diet. The most trustworthy experiments indicate that fat, starch, and sugar have not the least direct influence on the production of uric acid —but as the free consumption of these articles naturally

operates to restrict the intake of nitrogenous food, their use has indirectly the effect of diminishing the average production of uric acid. There may be, and indeed undoubtedly are, other differences between animal and vegetable articles of food, and between one article and another of the same class, which are highly important. They differ considerably among themselves in their digestibility, and in their stimulating qualities; but in regard to the point under review, namely, their direct influence on the production of uric acid, articles of diet must, as far as our present knowledge goes, be classified according to the percentage of albuminoid matters contained in them. As a rough guide in the choice of food for the gouty, the subjoined table may prove useful.

TABLE XVIII.—*Showing the Average Percentage of Albuminoid Matters contained in diverse Articles of Food*[1]

Animal food	Per cent.
Butcher's meat	19
Fowl	20
Game	22
Fish	17
Egg	13
Milk	4
Cheese	30

Vegetable food	Per cent.
Bread	8
Oatmeal	12
Rice	6
Green peas	6
Potatoes	2
Carrots and turnips	1 to 2
Green vegetables and salads	1 to 2
Fresh fruit (excluding nuts)	0·5 to 1

[1] This table was compiled from analyses given in Pavy's *Treatise on Food and Dietetics*, and in König's *Menschlichen Nahrungs-und Genussmittel.*

In choosing a diet for persons who are disposed to uratic precipitations, regard must of course be had to the whole condition, and especially to peculiarities of the individual. Nowhere perhaps is it more necessary than in gout to consider the man as well as the ailment, and very often more the man than the ailment—but the general rule in reference to the point under notice is, I think, pretty clear. Gouty people should be advised to partake cautiously of butcher's meat, fowl, game, and cheese, and to partake as freely as their digestion will permit of bread, rice, garden vegetables, salads, and fruit. The advantage to be gained from an adjustment of the dietary on these lines may be inconsiderable, or even inappreciable, in cases of inveterate gout; but it may be of critical moment in the slighter cases. A diminution of one or two grains per day in the amount of uric acid thrown into the circulation may make all the difference between the occurrence or non-occurrence of an arthritic attack.

The use of *alcoholic beverages*, as constituting an important feature in our dietetic habits, may here claim a word of comment. The most reliable researches indicate that these beverages in their legitimate use exercise no appreciable influence, either way, on the quantity of uric acid produced in the body. It was moreover found in my laboratory experiments that the addition to the medium of small quantities—such as might conceivably reach the circulation—of spirits, wines, or malt liquors, had not the slightest effect on the solubility of sodium bi-urate, nor any influence in accelerating or retarding the precipitation of the bi-urate in blood-serum impregnated with uric acid. The special and highly important part played by certain classes of alcoholic beverages in the genesis of

the gouty constitution, and in fostering a proclivity to uratic depositions, is evidently of a very subtle and complex character, and has apparently no direct reference to the chemical problems discussed in these lectures.

The use of culinary salt.—It was shown in the preceding lecture that no condition influenced the solubility of sodium bi-urate so conspicuously as the proportion of sodium salts in the medium. I observed, moreover, in my experiments on the maturation of blood-serum impregnated with uric acid, that the addition to the medium of small quantities of sodium chloride (0·1 per cent., or even less) always appreciably hastened the precipitation of the crystalline bi-urate. It has also been shown that the topographical distribution of uratic deposits through the body bears a striking relation to the percentage of sodium salts contained in the several organs and tissues. Indeed, it might apparently be said with truth, that if we possessed the power of regulating the dosage of sodium salts in the fluids and tissues of the system, we should be able effectively to control the occurrence of uratic depositions. Our power in this respect is, however, limited. These salts belong to the physiological constants of the blood, and their proportion therein can only be modified within a comparatively narrow range. These remarks apply especially to the most abundant of them, the sodium chloride. It has been found in experiments on animals that when common salt is given in excess with the food, or injected into the veins, the surplus is for the most part quickly removed by the kidneys, and there is only a small and transient increase of its percentage in the blood. And, conversely, when animals are fed with food abnormally poor in salt, there is only a slight

falling off in its proportion in the blood—but it almost disappears from the urine. The blood clings with great tenacity to its proper percentage of sodium chloride—and the experimental evidence indicates that in case of a threatened salt famine within the economy, the blood has the faculty of supplying its necessities by extracting salt from the less vital fluids and tissues—and contrariwise, in case of a glut of salt in the blood, the overplus is temporarily passed over into the serous cavities, until such time as the kidneys have succeeded in restoring the normal equilibrium.[1] All this leads to the inference that by lessening the intake of salt with the food we should abate its proportion in the blood only to a slight degree, but should diminish its proportion in the synovial fluids and fibrous tissues considerably. Acting on these ideas, I have been in the habit for some years past of directing gouty patients to restrict, as far as practicable, the use of common salt with their meals.

(*b*) ADMINISTRATION OF MEDICINAL SUBSTANCES

In forecasting the possible effects of medicinal substances given internally in the treatment of gout, it is well to fully realise the actual conditions of the problem. These are widely different from those presented to us in urinary gravel. In the latter case the daily dose is designed to form an addition to a comparatively small bulk of fluid, namely, to the forty or fifty ounces which constitute the diurnal discharge of urine. In the case of gout we are seeking to make an impression on a much larger bulk of fluid, namely, on the totality of the blood, lymph and synovia—a quantity in a man of average

[1] *Lavage du Sang*, by Dastre and Loye.—*Archives de Physiologie*, 1888, p. 93.

weight certainly not less than twenty pounds. Consequently, the effect of our dose must be proportionately less. Moreover, the urine is a dead excretion; it takes and keeps what is cast into it, and has no power of self-purification. The blood, on the other hand, is a living stream, with high powers of self-adjustment to a normal standard. A practicable dose of an alkaline carbonate enables us to radically alter the urine—to change its reaction from acid to alkaline, and thereby to exercise a decisive therapeutical effect in uric acid gravel. But the same dose only produces a feeble and transient effect on the mass of the blood and lymph; the blood passes on the surplus alkali with all speed through the kidneys into the urine, and quickly reattains its proper physiological standard of alkalescence.

The medicinal agents which have been chiefly employed in the treatment of gout, with a view of controlling the tendency to uratic precipitation, are the carbonates and phosphates of potash and soda, the carbonate of lithia, piperazine, and the waters of mineral springs—and it is to these alone that I propose to call attention.

Alkalies.—Alkaline substances are largely employed in the treatment of gout, both as pharmaceutical preparations and as components of mineral springs. It is widely believed that the alkaline carbonates and phosphates administered internally, by increasing the alkalescence of the blood, enhance its solvent power on the material of gouty deposits, and thereby delay or prevent their formation. The experimental evidence laid before you entirely destroys this hypothesis. It has been conclusively proved that alkalescence, as such, has no influence whatever on the solubility of sodium bi-urate. It has, moreover, been shown that the addition of an alkaline

carbonate to blood-serum impregnated with uric acid produces no appreciable effect on the process of maturation and the advent of precipitation of the crystalline bi-urate in the medium. The use of alkalies in gout has been advocated on another ground. It is held, in a vague sort of way, that there is an undue prevalence of acid in the gouty system, and that the blood is less alkaline than it should be. In some quarters it is even believed that this is the primary vice of the gouty state, and that there exists a so-called 'acid dyscrasia' which dominates the whole condition. I have been at some pains to ascertain what foundation there is for this belief; I have found very little of any kind, and none that is really valid. In the numerous examinations of the blood in gouty subjects made by Sir Alfred Garrod the serum was invariably found to be alkaline—never acid or even neutral. But he remarks that there is often (not always) a marked alteration in the degree of its alkalinity, and that in cases of chronic gout the serum sometimes shows a near approach to neutrality. It is, however, obvious that observations on the alkalinity of the blood have no validity in regard to the point under consideration unless they are made on cases of gout pure and simple. Gout is often complicated, not only with pyrexia, but with serious secondary lesions in the kidneys and joints, which lead to a profound cachexia. These secondary lesions bring with them blood-changes of their own, which are only remotely connected with the primary disorder, and have no bearing on the etiology of uratic precipitation. In the last few years some exact quantitative measurements have been made of the alkalinity of the blood both in health and in disease.[1] These

[1] See Peiper, in *Virchow's Archiv.*, 1889, and a paper by Rumpf in *Centralblatt f. Klin. Med.*, 1891.

researches indicate that a diminished alkalescence of the blood is a common pathological deviation; and that it occurs in a variety of conditions which have no special relation to gout—namely, in pyrexia, in diabetes, carcinoma, acute rheumatism, anæmia, leukæmia, and apparently in every kind of general cachexia. These facts and considerations suffice to show that, in the present state of our knowledge, the belief in an acid dyscrasia in gout rests on a pure assumption.

Lastly, the use of alkalies in gout is advocated on the ground that they facilitate the task of the kidneys in separating uric acid from the blood. The experimental evidence hitherto adduced on this point is so hopelessly contradictory that no conclusion can be safely deduced from it.

Clinical experience on the use of alkalies in gout speaks with a doubtful voice. I think I may say that few physicians have employed alkaline remedies in gout with more determination than myself. In years gone by I have repeatedly administered the bicarbonate and citrate of potash continuously for three and four years, and in sufficient doses to maintain the urine persistently alkaline, yet I have seen the arthritic attacks recur with apparently unabated regularity.

Carbonate of lithia and piperazine.—These medicaments have been introduced into the treatment of gout expressly on chemical grounds. Solutions of these substances possess a high solvent power on free uric acid; and it has been inferred from this fact that their administration internally might exercise a favouring influence on the solubility of sodium bi-urate in the bodily fluids, and thereby tend to prevent the formation of uratic deposits. This inference does not, however, appear to be justified. It was found experimentally that the addition of carbonate

of lithia or piperazine, in the proportion of 0·1 per cent. and 0·2 per cent., to blood-serum or synovia had not the slightest effect in enhancing the solvent power of these media on sodium bi-urate—nor the slightest effect in retarding its precipitation from serum and synovia artificially impregnated with uric acid. If these bodies have any beneficial action in gout, it is certainly not due, as has been supposed, to their solvent action on the material of gouty concretions.

Mineral springs.—The bearing of the inquiry on the use of mineral waters is, I think, of important practical interest. A considerable number of the springs to which gouty patients resort are strongly impregnated with the salts of soda. Now it has been conclusively shown that all the salts of soda act adversely on the solubility of sodium bi-urate and hasten its precipitation; and it may be inferred that the introduction of these salts into the circulation must tend to favour the occurrence of uratic depositions in the body. It is not, therefore, surprising to learn that not unfrequently the first effect of these waters on a gouty patient is either to provoke a downright attack of gout, or to aggravate the symptoms under which he was suffering. This event is now recognised by many physicians practising at these spas as a thing to be looked for; and experience has taught them the necessity of caution in regard to the quantity of the waters to be taken by newcomers. They comfort themselves and their patients, however, with the assurance that this preliminary storm is a necessary prelude to the calm amendment which is to follow. There is, no doubt, a solid foundation for this idea. It is no fiction that a gouty man, tormented with symptoms of irregular gout, is relieved by a regular arthritic attack. I presume that this arises from the complete, or approximately

complete, precipitation of the urates floating in his blood and lymph into the structures of the joints. The urates are thereby almost as effectually removed from the vital fluids as if they were eliminated by the kidneys. But it must, I think, be allowed that this is a rough mode of cure, and that it brings with it serious pains and perils of its own. My impression is that gouty persons should either entirely avoid springs which owe their activity to sodium salts, or should use them very sparingly. It is difficult to believe that they can do any direct good, and easy to believe that they can do direct harm. If they do any good at all, it must be indirectly, by acting on the liver and the intestinal tract.

There are, however, other springs of high and growing repute in the treatment of gout which are not open to these objections. These springs contain no soda, or only traces; and the sum of their mineral constituents does not exceed that which is often present in ordinary potable waters. They contain for their principal ingredient a little carbonate or sulphate of lime—and it is very doubtful whether the whole of this is absorbed into the blood; most of it probably passes out inertly with the fæces. In fact, springs of this class may practically be considered as equivalent to ordinary drinking-water, except that several of them have the advantage of being thermal. Among springs of this class may be mentioned: in our own country, the waters of Buxton, Bath, and Strathpeffer; in Germany, the waters of Gastein, Wildbad, Pfeffers, and the Sauerling spring at Carlsbad; in France, the waters of Aix-les-Bains, Contrexeville, Vittel, and Barèges. Now there can be no reasonable doubt that the efficacy of these springs has nothing to do with their scanty mineral ingredients, but depends on their watery constituent. They are drunk freely,

and on an empty stomach. Their action would be to temporarily dilute the blood, and lower its percentage of urates and sodium salts. This effect would tend to retard or prevent uratic precipitation, and thus give the defective kidneys additional time to overtake their arrears in the task of eliminating uric acid.

It may be asked whether the drinking of water at home would not answer as well as resorting to a mineral spring. The inference from my experiments is that, other things being equal, the beneficial results would be the same. But the 'other things' never are equal. It would scarcely be practicable for a man going about his usual business to drink eight or ten tumblers of water on an empty stomach every day for two or three weeks. At a watering-place the visitor has nothing to do except to attend to his 'cure.' Moreover, in getting away from home the invalid leaves behind him the worries of his daily life, and experiences the advantage of change of air and scene, with a salutary modification of diet, and he has abundant leisure for outdoor exercise. All these collateral influences help to raise the general level of health and quicken the action of the secretory cells. I don't think, therefore, that we can forego the advantages of the time-honoured practice of a visit to a mineral spring. At the same time, a word may be said in favour of a more systematic use of water in the everyday life of the gouty. I have observed that some gouty persons are very sparing in their use of diluents; such persons should be encouraged to be habitually more liberal in this respect. In a few cases it might even be possible to imitate, with plain water, the regular two or three weeks' course at the spa, and to repeat this course twice or thrice a year, as a prophylactic measure.

There is need of great caution in judging the effects

of therapeutical means in gout. The incidents of the diathesis, even in fairly typical cases, exhibit a waviness, a flux and reflux, which is very puzzling; and there is a normal tendency for the periods of aggravation to be followed by periods of amendment. In the less typical cases the irregularity of the morbid incidents is often such as to baffle all explanation. In most instances the manifestations become intensified with advancing years. But sometimes the converse is observed; the manifestations attain their maximum in middle life, and they may even entirely cease with increasing age. All these perplexing vagaries are within the compass of the natural history of the disorder; and, in assessing the value of remedies, it requires a good deal of sobriety of mind to avoid being deceived by fortuitous coincidences, or being made the dupes of our own preconceptions.

I believe that the most promising road to an improved therapeutics of gout lies through a fuller and more accurate knowledge of the chemistry of uric acid and the urates, and a more penetrating study of the reactions of these compounds with the fluids and tissues of the body. This is a large and difficult field of inquiry, and demands the co-operation of many workers. That is my apology for the fragmentary character of the present contribution. I shall, however, be quite satisfied with my share in the work, if what I have done prove an incentive and a help to other labourers in the same field.

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